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## Syme Memorial Lecture.[1]

### SURGERY OF THE HEART, PAST, PRESENT AND FUTURE.

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THE Syme Memorial Lectureship was founded by the Council of the Victorian Branch of the British Medical Association to honour Sir George Syme on his retirement from active practice in 1924, and before his death in 1929 he was present at the first lecture delivered by Mr. Fred Bird. All the men who have been privileged to deliver this lecture in the past had been closely associated with Sir George Syme as personal friends, colleagues, resident medical officers and students, and all spoke from full knowledge and admiration of the man and his works.

I saw him first after his return from the 1914–1918 War, and met him at a few meetings and heard him speak, but that is all, and I can add nothing to the high testimony to his greatness that has been given by previous lecturers. Anyone reading these lectures must marvel at the vast amount Sir George Syme accomplished in his lifetime and at the great part he played in raising the standards of our profession in this State.

[1] Delivered at a meeting of the Victorian Branch of the British Medical Association on April 18, 1956.

I should like to say how much I appreciate the honour of being invited to deliver the tenth triennial Syme Memorial Lecture, and I hope that the subject I have chosen will not be too boring to those who have gathered to do honour to a great man, whose name is becoming a legend and an example to those who follow on.

In 1938 Gross successfully ligated a patent *ductus arteriosus* for the first time, and this event marks the commencement of cardiac surgery as we know it today. Many men had speculated on the possibilities in this field and a considerable amount of experimental work had been done, but little had been achieved before 1938.

Pericardial paracentesis came into regular use in the early nineteenth century, and open drainage for suppurative pericarditis was introduced about 1875. In 1913 Rehn and Sauerbruck decorticated a heart for constrictive pericarditis, and by 1929 Churchill was able to find reports of 37 patients so treated. In 1896 Rehn reported the successful suture of a wound of the heart. Beck, in 1935, and O'Shaughnessy, in 1936, suggested surgical treatment for cardiac ischæmia, and although a vast amount of experimental and clinical work has been done since then, this problem is still unsolved.

Developmental deformities of the heart were little understood in 1907, when Munro suggested ligature of a patent *ductus arteriosus* to control subacute bacterial endocarditis, and worked out a practical technique. In 1913 Doyen attempted to use a tenotome, which he passed through the pulmonary artery to enlarge a stenosis of the pulmonary valve. Autopsy showed

that the patient was suffering from Fallot's tetralogy with an infundibular stenosis, and this operation was foredoomed to failure.

The importance of mechanical constriction in rheumatic valvular disease was recognized by Samways in 1898, and in 1902 Sir Lauder Brunton suggested a surgical attack on the stenosed mitral valve and was severely criticized for his temerity. Between 1923 and 1928 Cutler and Beck operated on seven patients with one survival. Allen and Graham, and Pridham, each attempted the operation once, and both patients died. In 1925 Souttar, in London, successfully dilated a mitral valve by passing his finger through the atrial appendage, and although he approached very near to the technique at present practised he did not again attempt the operation.

In 1914 Tuffier dilated a stenosis of the aortic valve by invaginating the aortic wall with his finger. The patient survived and was said to be improved; but it is difficult to believe that a significant aortic stenosis could be altered by this manœuvre.

In summary, it may be said that before 1938 the pericardium could be aspirated, drained or resected. Wounds of the heart with tamponade were being successfully treated in some centres, and attempts were being made by a number of surgeons to revascularize the heart in patients with coronary sclerosis. This was the state of heart surgery seventy years after Lister had revolutionized surgery in other fields.

Surgery is a mechanistic science, and to the surgeon the heart is an incredibly perfect pump, whatever it may be in poetry, religion or romance. In the average person it lasts for sixty to seventy years and beats over 31 million times each year. It cannot be stopped for running repairs or service. It cannot be reconditioned or rebored or replaced; but even this is not beyond the bounds of possibility. In early embryonic life it starts as a simple tube, and by an intricate process of development, becomes at last the fully-developed four-chambered heart. It is not surprising that congenital defects occur, or that inflammatory processes attack its delicate valves or that its arteries are not immune to the aging processes of arteriosclerosis.

Congenital defects of surgical interest take the form of obstructions to the flow of blood or abnormal openings between the right and left sides of the heart. Obstructions occur chiefly in the valves and out-flow tracts of the ventricles, resulting in pulmonary or aortic stenosis, and in the aorta, where the obstruction is called a coarctation. Abnormal openings occur between the two atria or the two ventricles, or between the aorta and pulmonary artery. Blood flows through these openings from the high-pressure left side of the heart to the low-pressure right side, and this useless leak increases the work that the heart has to do to maintain an effective circulation. When there is an obstruction to the flow of blood to the lungs, as well as an abnormal opening, the pressure on the right side of the heart may rise as high as, or higher than, arterial pressure, the shunt will be from right to left, and blood poor in oxygen will flow through the body, causing cyanosis.

Rheumatic fever frequently affects the heart valves, and especially those on the high-pressure left side of the heart, resulting in stenosis or obstruction of the mitral and aortic valves or in stretching and incompetence of the same valves. Inflammation of the pericardium, usually due to tuberculosis, may result in thickening and calcification of this membrane, constricting the heart.

The surgeon can enlarge a narrowed or stenosed valve, and this is needed chiefly for rheumatic stenosis of the mitral and aortic valves and for congenital stenosis of the pulmonary or aortic valves. He can cut out a coarctation and he can close abnormal openings, including patent *ducti arteriosi* and atrial septal defects. Defects of the ventricular septum can be repaired when the heart has been defunctioned and opened; but blind methods are unlikely to be satisfactory. All this has become possible since 1938, and it is of interest to review this period of development.

Since 1938 three phases of development are evident, and the dates of the principal advances are shown in Table I. (i) Between 1938 and 1948 cardiac operations were really extracardiac and performed on the great vessels. (ii) In 1948 Brock developed transventricular valvotomy for pulmonary stenosis, and Bailey, Harken and Brock all commenced to perform transatrial operations on the mitral valve. By 1950 the intracardiac blind techniques were accepted practices, and in a very short time a large number of patients had been operated upon. (iii) The year 1953 marked the beginning of open operations on the defunctioned heart, when Lewis successfully closed an atrial septal defect under hypothermia, and this has been followed by Lillihei's use of cross-circulation and dog-lung oxygenators and, finally, disposable plastic oxygenators for the closure of ventricular septal defects and *atrio-ventriculus communis* defects, and for the radical cure of Fallot's tetralogy. For the last twelve months Kirklin has been using a mechanical heart-lung machine to repair these same defects.

TABLE I.

*Development of Cardiac Surgery.*

| Year. | Procedure. | Worker. |
|---|---|---|
| 1938 | Closure of patent *ductus arteriosus.* | Gross. |
| 1944 | Shunt for Fallot's tetralogy. | Blalock. |
| 1945 | Excision of coarctation. | Crafoord, Gross. |
| 1948 | Valvotomy for pulmonary stenosis. | Brock. |
| 1948 | Valvotomy for mitral stenosis. | Bailey, Harken, Brock. |
| 1948 | Closure of atrial septal defect. | Gordon Murray. |
| 1952 | Valvotomy for aortic stenosis. | Bailey. |
| 1953 | Use of plastic valve for aortic regurgitation. | Hufnagel. |
| 1953 | Use of hypothermia for closure of atrial septal defect. | Lewis. |
| 1954 | Use of cross circulation for repair of ventricular septal defect, Fallot's tetralogy and *atrio-ventriculus communis.* | Lillihei. |
| 1955 | Dog's lung oxygenator for repair of ventricular septal defect, Fallot's tetralogy and *atrio-ventriculus communis.* | Lillihei. |
| 1955 | Heart-lung machine. | Kirklin. |
| 1955 | Simple disposable artificial oxygenator. | Lillihei. |

Surgical treatment for patent *ductus arteriosus*, coarctation of the aorta and mitral stenosis is so well established that I need spend little time discussing these conditions. The operation for closure or division of a patent *ductus arteriosus* is one of the most perfect in surgery and in the average case adds thirty to forty years to the patient's expectation of life, with a risk that should be a fraction of 1%. I believe operation should be advised as soon as a patent ductus is recognized, at any age under middle life, or at any age when it is causing disability.

Resection of a coarctation of the aorta is again a completely physiological operation; provided the aorta can be restored by end-to-end suture, relief should be complete and lasting. In a few patients, especially in the older age group, the divided ends cannot be approximated, and an aortic graft or a plastic prosthesis may be needed; in these cases long-term results cannot yet be assessed, but immediate results are excellent. Operation is best performed between the ages of ten and fifteen years, but may be required in infancy for the control of cardiac failure. Increasing age is now no contraindication, if symptoms warrant operation. Resection of a coarctation in a well developed adult is, I believe, the most exacting routine operation that has yet been devised. For this operation, and for the division of a patent ductus in an adult, we use "Arfonad", a hypotensive drug, to lower the systolic blood pressure to 70 to 80 millimetres of mercury. This makes resection and clamping of the great vessels much easier and safer, and certainly has a favourable effect upon the blood pressure of the surgeon and his assistants.

Rheumatic mitral stenosis is a common and crippling disease, and mitral valvotomy is now the most frequently performed and easiest of the intracardiac operations. The selection of patients for operation is often difficult; but in well-chosen cases a high proportion of excellent results is achieved. Many operations for mitral regurgitation have been devised, but none has proved effective.

## Fallot's Tetralogy.

Fallot's tetralogy is the condition most commonly present in "blue babies". There is stenosis of the pulmonary valves or the outflow tract of the right ventricle and an opening between the right and left ventricles, with an associated overriding of the aorta and hypertrophy of the right ventricle. Blue blood, which should go through the lungs to pick up oxygen, is shunted into the aorta.

Dr. Helen Taussig suggested to Dr. Blalock that, if some of this blood was directed back through the lungs, these children would be improved. In November, 1944, after extensive animal experimentation, Dr. Blalock joined the left subclavian artery to the left pulmonary artery in a seriously ill child with dramatic improvement, and in a very short time had completed a large series of these operations. In 1946 Willis-Potts suggested an alternative technique, by which an opening may be made between the aorta and the left pulmonary artery, and in 1948 Brock introduced his method of direct attack on the stenosis.

All these operations are only palliative and do not make the heart normal; but they do improve the exercise capacity of these patients enormously, and they do improve their colour and relieve them of the unattractive cyanosis. Children who were almost totally incapacitated are able to go to school and live nearly normal lives, and this operation earns more gratitude from patients and their parents than any other I know.

Only recently it was thought that it would be technically impossible to repair all the defects in Fallot's tetralogy; but in the last two years Lilliehei, using an open heart technique, which I will mention later, has done just this in a series of 17 patients with six deaths and 11 excellent results, and there now seems little doubt that this will become the standard method in the future.

### Pulmonary Stenosis.

Pure pulmonary stenosis is distinguished from Fallot's tetralogy by the absence of a ventricular septal defect, and for this condition shunt operations are useless and harmful. These patients may have an atrial septal defect, and when this is present they will be cyanosed. If there is no shunt, there will be no cyanosis.

Valvular pulmonary stenosis may be relieved by Brock's transventricular operation or by an approach through the open pulmonary artery. In order to open the pulmonary artery, the flow of blood must be stopped by closing the *venæ cavæ* where they enter the heart. This was tried a few times by Varco at normal temperatures, but the minute and a half during which blood flow could be safely stopped did not give quite enough time for precise operating. Swan has recently adopted this technique under hypothermia and has reported excellent results. If the stenosis is certainly entirely in the valve, open operation through the pulmonary artery would appear to be ideal; but Brock believes that an unrecognized infundibular stenosis is very often present and will be missed unless the ventricle is explored. Brock's method may stretch the valve but not always cut it, and Bailey has modified this technique by using a guillotine to hook up and cut the valve. Swan's technique may result in pulmonary regurgitation; but in two series of dogs whose pulmonary valves have been punched out the regurgitation produced has so far caused little disability, so this may not be an objection.

Infundibular stenosis or narrowing of the outflow tract of the right ventricle is more difficult to relieve than true valvular stenosis; but Brock's results are nearly as good for this condition as for valvular stenosis.

### Aortic Stenosis.

Aortic stenosis presents a vastly different problem from that of pulmonary stenosis. Entrance into the high pressure left ventricle is always hazardous, and the scarred, contracted, often calcified aortic valve is very different from the soft, pliable, stenotic pulmonary valve. First attempts at transventricular valvotomy were made by Bailey about 1952, and Brock and others were early in the field. It was soon apparent that, while aortic valvotomy was reasonably safe and satisfactory in patients who had both aortic and mitral stenosis, it was very dangerous and unsatisfactory when aortic stenosis was a solitary lesion. The left ventricle is protected by the reduced flow through a stenotic mitral valve, and its walls are less thickened and friable when both lesions are present. Because of the unsatisfactory results of transventricular valvotomy, Bailey in 1953 developed a technique for approaching the valve through a pouch of pericardium sewn to a slit made in a clamped-off segment of the aortic wall, and this approach, with the use of various types of pouches, has been adopted by Harken, Morrow and others, and has many advantages. The valve can be palpated and often split by the finger, and when relief seems hopeless the surgeon can retire in good order before he has produced a rapidly fatal regurgitation. Major causes of death from operation by the transventricular route are hæmorrhage from the friable ventricular wall and ventricular fibrillation, and both hæmorrhage and fibrillation are much less likely if the aortic approach is used. Bailey's results for the two methods reported in 1955, were as follows: (i) solitary aortic stenosis: transventricular approach, 68 cases with 19 deaths (28%); aortic approach, 41 cases with four deaths (10%). (ii) Aortic stenosis *plus* mitral stenosis: transventricular approach, 87 cases with 16 deaths (18%); aortic approach, 20 cases with one death (5%).

Recognizing the difficulty of restoring stenotic aortic valves, Sarnoff has been working on a technique to divert the blood from the apex of the left ventricle into the descending aorta through a plastic aorta and valve, and fantastic though this may seem, it may yet prove the most satisfactory solution. At his home I saw a fine collie dog capable of normal activity which had been living for nine and a half months with a shunt and valve of this type.

### Aortic Regurgitation.

For aortic regurgitation Hufnagal in 1953 described a plastic valve, which is inserted in the descending aorta below the left subclavian artery; 20% of his patients have died at operation and 20% later, but a few complete invalids were restored to activity. The defects of the technique are that clots form on the upper shelf of the valve seat and cause distal emboli, and that the valve hæmolyses blood, causing troublesome anæmia. It reduces the load on the left ventricle, but at the same time, by lessening the back flow, it reduces coronary flow during diastole, and the result depends on a fine balance between these factors. To place the valve more proximally would wreck coronary circulation.

### Atrial Septal Defects.

Atrial septal defects vary considerably in size and position in the septum; but if we exclude total absence of the septum and defects of the so-called *ostium primum* or endocardial cushion type, situated close to the tricuspid valve ring, and associated with defects of the mitral and tricuspid valves, the majority can be repaired by either closed or open heart techniques. Many methods have been suggested and used since Gordon Murray reported the first operation in 1948. In 1951 Gross, recognizing that atrial pressure was only two or three inches of water, developed a plastic well that could be sewn to an opening in the right atrium and filled with blood, so that the surgeon working through this pool of blood could feel the defect and stitch it up or apply a plastic patch. Bailey, in 1952, found that he could invaginate the dilated atrial wall into the defect and sew it to its margin, thus converting the right atrium into a doughnut type of cavity. With increasing experience Gross found that he could close most defects by simple suture from the outside with a finger in the atrium, and he has abandoned the well; but Kirklin of the Mayo Clinic has adopted it to sew into the defect a patch of "Ivalon" sponge, and he states that by this method he can repair all types of atrial septal defects. Conrad Lam uses an ingenious double-ended needle. Sonndergard, Crafoord and Bjork use a technique based on the passage of a purse-string suture through the septum and around the defect, and claim simplicity and success for this method. Lewis, Swan and Morrow are strong protagonists for open operation under hypothermia, and have reported excellent results. The view of the majority is that, for the present, closed methods are simpler and safer and should be preferred. Sometimes it is not easy before operation to be sure of the type of defect present, and palpation via the right auricular appendage should always be the first step after the pericardium is opened. *Ostium secundum* defects rarely cause severe disability in early life, and early breakdown nearly always means that the defect is not suitable for blind closure. In Lewis's series of 33 patients, 21 were aged over sixteen years and eight were aged over thirty years.

### Ventricular Septal Defects, Atrio-ventriculus Communis and Fallot's Tetralogy.

Although a few *ostium primum* defects have been closed without disaster, it seems better that they should be grouped with ventricular septal defects and repaired by deliberate open heart surgery by means of cross circulation or a mechanical heart-lung machine. At present hypothermia gives too little

time. So far, Lillihei and Kirklin are the only two surgeons who have had much experience of this type of surgery. Lillihei, starting with cross circulation and then a dog-lung oxygenator, is now using a simple disposable plastic oxygenator easily and cheaply constructed from materials available in any laboratory. Kirklin uses an elaborate heart-lung machine costing many thousands of dollars to construct.

Lillihei works on the azygos flow principle suggested by Andraesan and Watson working at the Buxton-Browne Farm in England. These workers showed that dogs would survive for prolonged periods with complete occlusion of the superior *vena cava* and the inferior *vena cava*, provided that the blood from the azygos vein was allowed to enter the right atrium. Cohen and Lillihei developed this principle, and showed that azygos flow in dogs was eight to 14 cubic centimetres per kilogram of body weight per minute. They experimented on 19 dogs, and all these dogs survived thirty minutes of inflow occlusion with only the azygos open; 17 of them recovered completely.

In human operations Lillihei and Cohen have aimed at a flow rate of 30 cubic centimetres per kilogram of body weight per minute, and found it completely adequate in every case. In view of the pioneering nature of this work, the desperate condition of many of the patients and the severity of the interference, Lillihei's results shown in Table II are very impressive.

TABLE II.

*Direct Vision Intra-Cardiac Surgery: Walton C. Lillihei.*

| Method Used and Procedure. | Number of Patients. | Number of Deaths. |
|---|---|---|
| Cross circulation: | | |
| Closure of ventricular septal defect | 26 | 7 |
| Radical cure of Fallot's tetralogy | 11 | 4 |
| Closure of *atrio-ventriculus communis* | 3 | 2 |
| Solitary infundibular stenosis | 1 | 0 |
| Pulmonary stenosis with atrial septal defect | 1 | 1 |
| Dog's lung oxygenators | 4 | 3 |
| Disposable artificial oxygenators: | | |
| Ventricular septal defect | 25 | 7 |
| Fallot's tetralogy | 6 | 2 |
| Atrial septal defect / *Atrio-ventriculus communis* / Transposition of great vessels | 5 | 0 |
| Total | 82[1] | 26[1] |

[1] The last 19 patients with two deaths.

### Hypothermia.

Swan believes that hypothermia is satisfactory for open operations on the right side of the heart that can be completed within eight minutes. This limits it to closure of atrial septal defects and open operation in pulmonary valvular stenosis, although Scott once succeeded in repairing a Fallot's tetralogy by this method in seven minutes. In several others he was unable in the time to perform more than an infundibulectomy. Hypothermia is also used by Swan, Bigelow and Mustard, and some others for standard cardiac procedures in "poor risk" patients, and for non-cardiac procedures when hypertension or prolonged local circulatory occlusion is anticipated. Ventricular fibrillation is frequent and difficult to control in the cold heart, and still remains a real stumbling block to the general use of hypothermia for cardiac operations.

### Coronary Disease.

The value of surgical treatment for coronary artery disease is difficult to assess. Those who have particularly interested themselves in this problem are convinced that satisfactory anastomotic blood vessels can be developed, and will protect dogs from death after ligation of the anterior descending branch of the left coronary artery. Many operations have been performed, and it is claimed that bed-bound patients with angina regularly leave their bed and lose their pain. Unfortunately, no objective evidence of real improvement in dogs or humans has been presented. Beck has abandoned his method of arterializing the coronary sinus, but is still enthusiastic about the benefits of poudrage with asbestos dust after removal of the epicardium with a burr. Dwight Harken does the same thing with 95% phenol solution. Vineberg buries the bleeding internal mammary artery in the myocardium, and many surgeons use poudrage as originally recommended by Thompson. I do not know, but I should hesitate to say, that the results claimed are all due to sledge-hammer psychotherapy.

### Conclusion.

At the Alfred Hospital we have operated on 616 patients for cardiac diseases and Table III summarizes our experience.

TABLE III.

*Cardiac Operations at the Alfred Hospital, Melbourne.*

| Procedure or Condition. | Number of Patients. | Number of Deaths. |
|---|---|---|
| Pericardial resection | 17 | 1 |
| Patent *ductus arteriosus* | 191 | 1 |
| Fallot's tetralogy *et cetera* | 190 | 22 |
| Coarctation | 63 | 5 |
| Pulmonary stenosis | 15 | 2 |
| Mitral stenosis | 122 | 6 |
| Aortic stenosis | 2 | 1 |
| Atrial septal defect | 6 | 3 |
| Vascular ring | 4 | 0 |
| Pulmonary aortic fenestration | 2 | 1 |
| Coronary sclerosis | 2 | 0 |
| Total anomalous pulmonary veins | 1 | 1 |
| *Ectopia cordis* | 1 | 1 |
| Total | 616 | — |

It is not intended to review these cases in detail, as this is being done in another paper to be published shortly. Table III is included to show that the risk to life with these operations compares favourably with that of other operations of the same magnitude.

Up to the present, certain conditions have defied all attempts at surgical relief. Notable among these are complete transposition of the great vessels and mitral regurgitation, and the position of aortic stenosis and regurgitation is very little better. Some success has followed attempts to correct anomalous pulmonary venous drainage, and Mustard is to be congratulated on the successful treatment of three babies with this condition. Surgical relief for these conditions must await the full development of methods to exclude the heart from the circulation for a sufficient period to allow deliberate correction of these major disabilities. There are some defects that are mechanically beyond the possibility of modification, and it may be that in time we shall be able to remove the heart and replace it by another, as is now done with arterial segments. Fantastic as this may seem, it should be to us no more absurd than many of the things we do today would have seemed to surgeons of even fifty years ago, if they had visualized the possibilities.

The eighteen years since Gross closed the first patent *ductus arteriosus* has been a period of tremendous developments in many fields. It has seen the splitting of the atom, the development of electronics, jet engines, plastics and antibiotics. Heart surgery has made amazing strides and is still advancing, and who knows what miracles we may yet see? The heart-lung machine seems destined for great things and, with the vast potential of modern scientific and industrial research, it may soon revolutionize our approach to many problems.

## PROTEIN DIGESTS IN THE TREATMENT OF ALLERGIC DISEASE.[1]

By C. T. PIPER,
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IN THE MEDICAL JOURNAL OF AUSTRALIA of February 28, 1955, there was a paper by me on the experimental treatment of hay fever. The following is an account of further results with this method during a special twelve months' observation.

[1] Synopsis of a paper read at a meeting of the Australian Society of Allergists, Sydney, August, 1955.

During this time we applied this treatment to 827 patients in my private and Children's Hospital clinics. All these patients were carefully observed and followed up to the end of the period as far as possible by myself, and finally dispassionately assessed as to the degree of improvement and the worthwhileness of the result. In the end 722 patients were included in the analysis, the result of the others being unknown; routine of treatment and recording were carried on by my assistants and nursing staff. The method was applied to practically all patients in whom significant allergic nexus was present.

Every care was taken to ensure a dispassionate assessment. Primarily this assessment was made to determine whether I should go on using this treatment or not. All other considerations apart, my own selfish interest demanded this; this principle was varied only to write down rather than up. Cases of pure pollinosis were assessed by an end-of-season *questionnaire*, all others by clinical observation and verbal discussion. This latter method was applied also to the grass pollinosis group, and it was found that our assessment by this method tallied reasonably with the assessment of the patient; this indicates that our assessment of the other groups considered is within reason correct.

The number of patients in each group are in my opinion sufficient to be statistically significant; this is confirmed by the report from the Commonwealth Scientific and Industrial Research Organization statistician's report.

A control series was not established, so that this document is a clinical report only. There is, however, what one may call the control of experience. In four years of intensive study and practice of allergy I have not seen results like these with any other method, and only two writers have claimed them: Auld, with his discredited peptone, and Phillips, who was mentioned in my earlier paper.

It is the habit of the allergophobe to lay all allergic diseases at the door of psychopathy and to discount the claims of the allergists on that account. The various implications of this have been kept in mind in the application of this treatment and in assessment. The effect of coincidental treatment was also fully considered in the assessment.

The result of the analysis is that I and those who have worked with me for years are satisfied that we have a new method of attack on allergic disease which we must continue to use. We are quite satisfied that seven out of ten of our patients will have worthwhile benefit from its use; that we have a reasonably satisfactory co-seasonal treatment for hay fever which does not respond to antihistamines; that we can expect to give sufferers from perennial allergic rhinitis or asthma, or both, relief from symptoms in two weeks; and that we can approach the problems of atopic dermatitis and chronic urticaria with confidence instead of our precedent pessimism. We are also satisfied that this method has reduced very considerably the need for formal desensitization in many cases, and that many patients successfully treated by this method are better to have formal desensitization as well in order to attain lasting benefit; we frequently advise them so and prescribe it.

The advantage which the method confers in respiratory allergy not due to pollens is that it gives results with five injections in ten days which formal treatment will not give in less than ten weeks. During the period of four months, which seems to be the average expectable period of relief by this method, desensitization may be completed with its average expectable relief period of some years. These responses are of course highly variable and individual.

Having made this assessment of something new for our own purposes and found it good, we considered that this method should be investigated by those with ample capacity to apply scientific instead of clinical methods to it. This involves series of thousands, not hundreds, with parallel controls, and research into the metabolic and biochemical phenomena associated with it. These things not being within my scope, it became my duty to publish with the object of interesting someone able to do these things, the proper place of first publication being the Australian Society of Allergists. To this end I invited the Society to hold a meeting in Adelaide, so that I could report results and show my cases, but this could not be arranged. It became necessary, therefore, that I should present my very full analysis at the pre-congress meeting of the Society in August. This piled up to 21,000 words and, as one could expect only to meet considerable incredulity, there were included 81 case reports. I would add that unless I had seen these things happen repeatedly with this treatment I would not have believed the story myself.

The Editor of THE MEDICAL JOURNAL OF AUSTRALIA has asked, and quite properly, that I reduce the paper to one-quarter of its original length. This is done here, but that reduction means the elimination of case reports and the statement of conclusions without argument. I would ask the critic to bear this in mind and to remind himself of my primary motive in making the analysis of which this is the outcome. He may then be assured that I am certain of the validity of my figures and conclusions.

The method of treatment is much as is set out in my previous paper—the intradermal injection of such a dose of solution as to produce a weal of one centimetre with a surrounding erythema of two centimetres, and the administration of five such treatments at intervals of two days; although in urgent cases we have given them at two-hourly intervals and so treated our country hay fever patients in two days and let them be home in that time. We then wait a fortnight. If there is no improvement then we give up the treatment as a failure; if there is some improvement, but not enough, we give more doses at weekly intervals until stability is reached (usually three). If there is adequate improvement, we wait to see. If relapse occurs, we repeat as many injections as are necessary to give relief; some patients are put on to regular maintenance therapy.

The first dose is 0·01 cubic centimetre of 1% strength of all allergens for children and of pollens for adults; the other common allergens are given to adults in a first dose of 0·01 of 10% solution unless a high degree of reactivity is suspected. The subsequent doses are gauged by the reaction to this first dose, and experience teaches what it should be. The bogy in all treatments is generalized histaminosis, as previously described. This applies the same limitation to the general use of treatment as was indicated in the previous article. It is on this account that I have had to refuse requests for these extracts from distant practitioners, and a small experiment in farming out these substances to some general practitioners in 1954 has justified me in this.

The solutions we use are made by digesting ten grammes of crude ether-washed allergens with 70 cubic centimetres of N/10 hydrochloric acid solution and one cubic centimetre of glycerine of pepsin; the filtered residuum is neutralized, carbolized and brought to 100 cubic centimetres; it is thermostable and apparently bacteriostatic. Our process is crude by scientific measures but gives a standard product on a standard technique.

We have prepared these solutions from pollens of several grasses and flowers, individually and as mixtures, from house dust, feathers, kapok, wool, chaff dust, horse, cat, dog, rabbit, cattle and guinea-pig danders, egg white, gluten, oyster, crab, crayfish, tomato mould and penicillin. We use them separately, in combination giving two treatments simultaneously, or in mixtures. These mixtures correspond to the extract mixtures used in formal treatment, although there is one we call "doman", which contains all the domestic and animal allergens and which has given many satisfactory results in the multiple-reacting child.

It is our usual practice now to start formal desensitization with an appropriate stock mixture of 1/100,000 strength in association with this digest treatment; if the patient has to go on to formal treatment no attendance or time is then wasted. I am sure that these doses have not affected the result. We have also gradually substituted

the reaction to these solutions for routine intradermal tests, especially in children in whom such tests are not desirable. It has proved quite safe to give four such minimal test doses at one time. We thereby give a first treatment and can more quickly find an appropriate treatment solution. For it is our conclusion that where there is a skin reaction to one of these digests in a patient with a tallying history it is very probable that a course of such digests will do a great deal of good.

This brings up the matter of specificity; we are still in doubt on this, as we have had many experiences which indicate that adequate reaction and not specific digest is the determining relieving factor.

## RESULTS.

Let us now turn to consideration of results.

### Co-Seasonal Treatment of Grass Pollinosis.

In the co-seasonal treatment of grass pollinosis the patients are divided into two categories. They were all treated in my private clinic and practically all suffered from severe conditions not able to be relieved by medication. All were fully informed that this was a new and experimental treatment and that not more than three out of five would obtain adequate relief. This, apart from being a proper thing to do, would help dispel any nexus of suggestion. They were also advised by pamphlet of the nature of formal desensitization and of the generally published prognosis therewith. In *questionnaires* sent at the end of the season they were asked to indicate whether they would prefer to have pre-seasonal treatment in 1955. This *questionnaire* was necessary for me to complete my advice to them on their future management, and the patient was advised of this. It is this which accounts for the high *questionnaire* return (80%).

In the first category were 227 patients certainly affected by grass pollinosis and by it alone. From these we had 197 assessable replies. The other 30 were added to the 57 in the second category who had a complicated picture, but who were treated with grass pollen digest, as they were also sensitive to grass pollen. In the people in this category we could not be sure that grass pollinosis was a major factor; so they were not circularized, but were assessed by our knowledge only.

Patients in the first category were asked to assess their relief as nil, 25%, 50%, 60%, 75%, 90% and 100%. Arbitrarily I set 50% or more as a worthwhile result and anything below it as a failure. I am satisfied that this figure is a correct one. Firstly, this is indicated by our own knowledge of many people who acknowledged 50% relief; of 44 of these people chosen at random I was satisfied that 38 had had good results from their treatment. Secondly, comparison with figures attained in the parallel *questionnaire* to people who had had pre-seasonal treatment showed that many were quite satisfied with a 50% result from it. Thirdly, 28 of this group answered "yes" and six "no" to the question "Did the treatment relieve you enough to control your hay fever with an occasional pill on a very bad day?". Such a degree of control with this type of hay fever is in my opinion quite a good result, for hay fever readily controlled by antihistamines does not require any other treatment. The result is as shown in Table I.

This makes an average improvement of 59·4% among 197 patients, and among the 76% of patients with a worthwhile relief an average of 73%; one-half of the patients obtained very good relief and one-quarter obtained excellent relief.

The average number of treatments given to all patients was 5·6; the average to relieved patients was 5·3 and to unrelieved patients 6·3; the minimum to a relieved patient was 3 and the maximum was 15. Forty-four relieved patients had seven or more treatments; eight of them had ten or more.

Practically the same number of patients obtained excellent relief as experienced failure in treatment. This would make this simple treatment worth while as an emergency treatment provided that there was no risk to life and minimal risk of making the patient worse. After experience in some 2000 cases I am quite sure that there is no risk to life or of severe reaction with this treatment if due care is observed. Seven patients claimed that they were worse; two of these were better, not worse, as shown by reduction of disability as the season came to its peak; one was suffering from ingravescent hay fever and would have been worse without the treatment; the other four were severe intractables. These people, the ones which one can "cure" only with steroids, form a definite clinical group; they have in my opinion a quite different disease from the general run of allergics and, possibly significantly, are nearly always made much worse temporarily by this method of treatment, whatever the allergen concerned may be.

TABLE I.

| Degree of Relief. | Number of Patients. | Summary of Result. |
|---|---|---|
| Nil | 27 | 45 failures (23%). |
| 25% | 18 | |
| 50% | 38 | 50 worthwhile=one *plus* (29%). |
| 60% | 12 | |
| 75% | 53 | 58 good=two *plus* (26%). |
| 80% | 5 | |
| 90% | 34 | 44 excellent=three *plus* (22%). |
| 100% | 10 | |

Analysis of the time of treatment indicated that five treatments given in September would achieve the same average results as five in later months. If less than five were given in September, the need for boosting doses through the season rose sharply. If the treatment worked in September, then boosting doses would relieve the condition again; if it did not, then further treatment was valueless.

The duration of relief varied from a few days after each injection to the whole length of the season. Thirteen patients who were not responding were "topped up" with intravenously administered peptone. Only two did not obtain good help from this, two had to have six injections to obtain a good result, and the others were well after one to three minimal doses.

Ten patients were treated who had experienced failure with pre-seasonal treatment, and six obtained satisfactory results.

#### *Relief of Asthma.*

In this series 72 patients had asthma; 67 had certain pollen asthmas, and of these 55 were adequately relieved of their asthma; in many cases the asthma disappeared, but the rhinitis did not.

#### *Comparison with Pre-Seasonal Treatment.*

A *questionnaire* was sent to a random 200 patients on our pre-seasonal list and 72 answers were received for analysis, sufficient for a rough evaluation only. The comparative assessment is as shown in Table II.

Of the relieved group 41 patients were analysed who previously had had pre-seasonal treatment; three said that pre-seasonal treatment was more effective, and 11 claimed a better result with the digest treatment; the others did not answer the question. In 14 of our failures the patients had previously had failure with pre-seasonal treatment.

I believe that digest and formal treatment both will relieve the same patients and that digest treatment will relieve very few for whom well-conducted pre-seasonal treatment fails.

#### *Patients in the Second Category.*

An analysis of our impressions of the treatment of patients in the second category shows the following: failures, 18; unassessable, 24; one *plus* (50% to 60%), 24;

two *plus* (75% to 100%), 21. That is, of known results 45 were worth while and 18 were not.

*Conclusions.*

There is no other co-seasonal treatment of which I know which will give results in these conditions approaching those indicated by these figures. I therefore feel amply justified in continuing to use this treatment in my practice. We still, however, have our troubles with general reactions. In these circumstances I do not feel justified in giving this material or recommending the use of it to those practitioners who have not had some training in its use. During this year we have trained some 12 doctors who have been sufficiently interested to give the time to it. Our requirements in this matter are that they should spend at least three full half-days in our treatment centre in the season. The Commonwealth Serum Laboratory has been given the formula and will release the material at its discretion.

TABLE II.

| Degree of Relief. | Number of Patients. | |
|---|---|---|
| | Pre-Seasonal Treatment. | Treatment with Digest. |
| 100% .. | 5 (7%) | 10 (5%) |
| 90% .. | 6 (8%) | 34 (17%) |
| 80% .. | 28 (40%) | 58 (31%) |
| 60%, 50% .. | 15 (21%) | 50 (26%) |
| Less than 50% | 18 (25%) | 45 (24%) |
| Total .. | 72 | 197 |

## Respiratory Allergy Not Due to Spring Grasses.

Cases of respiratory allergy not due to spring grasses are all assessed by clinical observation in the grades of "*plus*" as illustrated above. The following results were obtained with the compositea group of pollens: cases treated, 17; failures, 2; one *plus*, 6; two *plus*, 8; three *plus*, 2.

In this limited series the percentages above are repeated. In cases of flower-pollen asthma I am prepared to promise relief with three daily doses. We treated eight patients suffering from late summer hay fever due to plantain or couch-grass pollen; six of these had excellent results.

TABLE III.

| Result. | Preseasonal Group. | Digest Group. |
|---|---|---|
| Average relief in all cases .. .. | 60% | 59% |
| Number relieved to 50% .. .. | 75% | 76% |
| Average relief in those relieved to 50% | 76% | 73·5% |
| Maximal relief .. .. .. .. | 15% | 22% |
| Failures .. .. .. .. | 25% | 24% |

## Respiratory Allergy Not Due to Pollens.

Patients suffering from respiratory allergy not due to pollens (perennial allergic rhinitis, spasmodic asthma and combinations of both) respond in equal degree; and where they are combined it is quite usual for either or both of the symptoms to disappear.

Domestic and animal allergy respond equally, and we have had dramatic and very satisfying results in cases of long-standing disease.

It is the expectation now in my clinics that we will send the majority of our asthmatics back to their own doctors at the end of a fortnight fully relieved of persistent trouble for four months by means of this treatment.

The average expectation of relief, when gained, is four months, but as at July, 1955, we had one adult who after two courses of five treatments had had relief of symptoms for seventeen months, and eight children at least who had been quite free of persistent disabling asthma for at least eight months, and five who had been free for eleven months. We have found it necessary to give fortnightly maintenance doses in several cases, and this method has succeeded with them when other treatments have failed. Relapse after previous successful desensitization is effectively controlled. One patient with physical asthma who was treated did not respond, and the treatment did not relieve proven intractables; indeed, it made some of them worse, these being of the "cortisone" type, as in the pollen cases.

The cyclic asthmatic bronchitis of children was not fully controlled, but the attacks were modified and less severe; in one case of superficial punctate keratitis of eight years' standing, ingravescent and nearly crippling, the patient was fully relieved by five experimental treatments and remained so on fortnightly maintenance.

We assessed 315 of these cases with the following results: failures, 103; one *plus*, 63; two *plus*, 107; three *plus*, 42. The proportion of failures was 32%. Twenty-five more patients were improved, but it was not certain that other circumstances were not responsible for the improvement.

## Dermatoses.

*Urticaria and Angiodema.*

I reported four cases of complete and lasting relief from urticaria and angiodema when the patients were treated with house dust, egg, gluten, dog hair, and sea-food digests respectively.

Thirty-one patients were treated and 28 assessed with the following results: failures, 8; one *plus*, 3; two *plus*, 11; three *plus*, 6.

I think we get about these same results with long courses of vaccines. The majority of the patients were treated with the mixture of gluten, milk and egg digests, and the patients were principally children. Avoidance of the allergen was not insisted on, and test exposure was actively encouraged; it is to be noted that of ten adults treated only two obtained material improvement.

*Atopic Dermatitis.*

We treated 115 patients suffering from dermatitis and were able to assess 99. Only 28 did not obtain a good measure of help; in 13 of the 28 cases the likelihood of atopic origin was not great, but the treatment was used on a speculative basis. Many patients who responded had a severe form of the disease, and several could be classed as "dermatologists' failures". For purposes of assessment the cases fall into five classes. In all the first four classes very good results were attained and cases have been reported. The classes were as follows: (i) Cases of pollen dermatitis with a clear pollen nexus. (ii) Cases with no clear pollen nexus, in which there may or may not be a positive response to scratch tests to pollens, but in which significant wealing results from the intradermal injection of pollen digest and the reaction is probably non-specific. (iii) Cases of domestic, animal and chaff sensitivity, in which specific treatment is applicable. (iv) Cases of food eczema, in which a significant reaction occurs to the digests of egg white, milk protein and gluten. (v) Cases in which the treatment is not likely to succeed; this includes those in which the patients will not yield a significant reaction to any digest or, although they have proven allergies, have a major psychological factor in their disease.

Particularly interesting were the cases in the second class. The action of compositea pollen digest here is certainly non-specific in many cases. Compositea digest is clinically very diffusible, and there is greater likelihood of histaminosis with it than with any other.

It is our belief that we can take the sting out of any severe atopic dermatitis after three days if we can get an adequate reaction to compositea toxoid.

We treated only eight patients suffering from infantile eczema and did so very gingerly. I am quite satisfied that

five patients obtained definite benefit, two having complete clearance not attributable to other causes.

The residual patients with infantile eczema responded uniformly well to the egg, milk, gluten mixture. We have had many quite remarkable improvements in this disease.

The use of these agents has quite changed our outlook in the treatment of dermatoses. The results with atopic dermatitis were as follows: failures, 28; one *plus*, 19; two *plus*, 34; three *plus*, 18.

### CONCLUSION.

It is my wish in publishing this to interest those who can take the matter further. The only claim that is made is that the analysis is dispassionate and the story true. I should be glad to give more details to anyone interested who can really carry out the work as I suggest. It is at present a somewhat expert method—it is not to be used in a casual way—and those who use it to treat hay fever will have their tribulations and disappointments, however great their experience; but those who persevere will find it well worth while.

## THE EFFECT OF POLY-VINYL-PYROLLIDONE AND TETRA-HYDRO-AMINOACRIDINE ON THE MORTALITY AND SURVIVAL TIME OF MICE INJECTED WITH SNAKE VENOM.

By E. R. TRETHEWIE.[1]

*From the Department of Physiology, University of Melbourne.*

APART from local and general non-specific measures, antivene therapy is as yet the only specific available for the treatment of snake-bite poisoning due to neurotoxic and cardiotoxic venom. Since neurotoxin is the main lethal agent in a large number of snake venoms, and since this is especially true of Australian snake venom, therapy designed to reduce the toxicity of neurotoxin should form a major advance in treatment. It is true that some other forms of therapy have been shown to be of value experimentally with other venoms; for example, heparin in the case of *Echis carinatus* and Russel viper (Ahuja, Veeraraghavan and Menon, 1946; Ahuja, Brooks, Veeraraghavan and Menon, 1946) which being viperine is largely a clotting venom. Heparin and antihistamine have also been used to counteract the venom of the Australian black snake, *Pseudechis porphyriacus* (Trethewie and Day, 1948*b*), but this latter venom, which is a clotting venom and a powerful releaser of histamine (Trethewie, 1939) is only feebly neurotoxic and rarely causes death except in infants. Further, heparin was found to prolong the survival time of the extremely potent neurotoxic venom of *Notechis scutatus* (Australian tiger snake) (Trethewie and Day, 1948*a*), but the mortality was quite unchanged. Artificial respiration likewise only prolonged the survival time (Silberberg, 1954). The mortality from severe snake bite is approximately 50%. In Australia yearly about six people die from this condition. The estimated mortality for the world, excluding the U.S.S.R., China and Central Europe, is 30,000 to 40,000 annually.

Schubert (1954) produced evidence to show that poly-vinyl-pyrollidone reduces the toxicity of diphtheria toxin and tetanus toxin. Since both these toxins are neurotoxic it was thought worthwhile to examine the effect of this colloid on the mortality from snake venom. The colloid might also be expected to reduce the mortality from cardiotoxin. Cobra venom was chosen for these experiments, as the survival time after injection of the venom is usually only three to twenty-four hours. Differences might be detected more readily by this method than by using venom of the tiger snake, after which death may be delayed for several days (Trethewie and Day, 1948*a*). The work is now being repeated for tiger snake venom. Further, the effect of tetra-hydro-aminoacridine, which has powerful neurological effects, on the mortality from neurotoxic venom was thought worthy of investigation, especially as this compound is a respiratory stimulant (Bentley, 1952). It is also an anti-esterase and is atropine-like in action (Shaw and Bentley, 1953). Earlier work with monoaminoacridine revealed no significant reduction of either the mortality or the death time resulting from cobra venom (Trethewie and Day, 1948*c*).

### Method of Investigation.

The mice used in these experiments all belonged to one mixed ("Swiss" mixed) interbred strain, except for one group of brown mice, which was divided into two equal groups for an individual experiment with its control. The mice weighed from 16 to 25 grammes and experiments were carried out with equal numbers in control and treated groups on each occasion. Mice were injected alternately either with treatment drug or with control saline after inoculation with venom. Venom injections were made strictly subcutaneously over the right lower quadrant of the abdomen, and subcutaneous treatment injections (or saline controls) made subcutaneously over the left lower quadrant of the abdomen. Poly-vinyl-pyrollidone was injected intraperitoneally, as was the control injection in these instances. The mice were kept in cages side by side, over a warm plate, in a fan-ventilated room and supplied with water and food pellets, and survivors were killed on the eighth day.

The venom used, Indian cobra (*Naja-Naja*), was from two sources. One portion was obtained from the Walter and Eliza Hall Institute. This venom had been maintained in a potent condition by having been vacuum dried and tube stored. Later experiments were carried out with similar venom obtained from the Commonwealth Serum Laboratories, Melbourne. This latter venom was a little more potent; approximately one milligramme of the Walter and Eliza Hall venom equalled in activity 0·8 milligramme of the Commonwealth Serum Laboratories venom.

Either the poly-vinyl-pyrollidone (PVP) was used as "Plasmosan" solution (35 milligrammes in one millilitre of Tyrode-like solution), or the "Plasmosan" was freeze-dried and the PVP so obtained was redissolved in distilled water (50 milligrammes in one millilitre of solution) before use. Control solutions used were either saline or Tyrode. These control solutions produced no significant effect on the toxicity of the venom. Tetra-hydro-amino-acridine (THA) was supplied by Nicholas Proprietary, Limited.

### Experimental Work.

#### 1. *Effect of Saline on the Mortality and Survival Time of Mice Injected with Venom ("Swiss" Mixed Mice).*

Sixteen mice (17 to 25 grammes) were injected subcutaneously with one milligramme of cobra venom (Walter and Eliza Hall) per kilogram of body weight. Eight of the mice were also injected intraperitoneally with one millilitre of sterile saline. All 16 mice died. The saline-injected mice died in 116 to 355 minutes (average 180 minutes) and the remainder died in 105 to 233 minutes (average 155 minutes).

These findings are represented graphically in Figure I, where the interrupted line (open dots) shows the findings with venom alone, and the continuous line (closed dots) shows the findings with the saline-treated mice. This difference in survival time is not significant statistically ($P = 0{\cdot}4$). Thus the intraperitoneal injection of saline in a volume of one millilitre had no significant effect.

#### 2. *Effect of Poly-Vinyl-Pyrollidone on the Mortality and Survival Time of Mice Injected with Venom ("Swiss" Mixed Mice).*

Sixteen mice (17 to 25 grammes) were injected subcutaneously with one milligramme of cobra venom (Walter and Eliza Hall) per kilogram of body weight. Eight of

[1] Technical assistance for this work was aided by a grant from the Australian National Health and Medical Research Council.

these mice were injected intraperitoneally with one millilitre of sterile saline (the group referred to in paragraph 1), and eight were injected intraperitoneally with 35 milligrammes of PVP in one millilitre of polyvidone solution. All 16 mice died. The saline-injected mice died in from 116 to 335 minutes (average 180 minutes) after injection, and the "P.V.P. *plus* saline" injected mice died in from 100 to 368 minutes (average 245 minutes) after injection.

This difference in survival time is significant statistically by the analysis of variance. These findings are represented graphically in Figure I, where the continuous line (closed dots) shows the findings with the saline-injected mice and the interrupted line (closed dots) shows the findings with the PVP-injected mice.

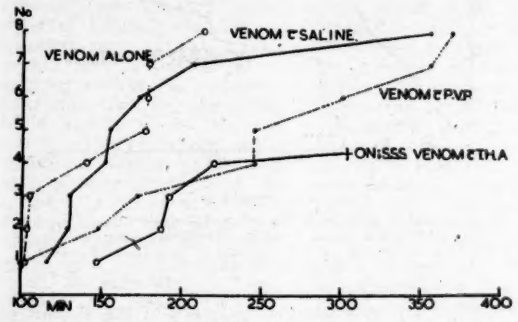


FIGURE I.

Survival times in a series of "Swiss" mixed mice injected with cobra venom. ON: overnight death. S: survival. Ordinate: number of mice. Abscissa: survival time in minutes. Further details in text.

The experiment was repeated on 31 "Swiss" mixed mice with Commonwealth Serum Laboratories cobra venom. Sixteen mice (16 to 25 grammes) were injected with 0·7 milligramme of venom per kilogram subcutaneously and one millilitre of Tyrode intraperitoneally. Fifteen mice were injected with 0·7 milligramme of venom per kilogram subcutaneously and one millilitre of polyvidone solution (containing 35 milligrammes of PVP) intraperitoneally. One mouse had been discarded from this group (originally 16) since the venom leaked from the injection site. In the control group 15 mice died in from 128 to 817 minutes after injection (Figure II, upper line). One mouse survived. In the treated group 12 mice died in from 138 to 1388 minutes after injection (Figure II, lower line). Three mice survived.

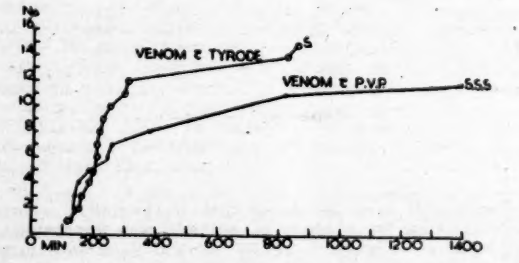


FIGURE II.

Survival times in a series of "Swiss" mixed mice injected with cobra venom. S: survival. Ordinate: number of mice. Abscissa: survival time in minutes. Further details in text.

The prolongation of survival time attained with PVP was therefore again evident, and this difference was highly significant statistically. Of the 24 control mice in this series one survived, while of the 23 treated mice three survived.

### 3. *Effect of Tetra-Hydro-Aminoacridine on the Mortality and Survival Time of Mice Injected with Venom ("Swiss" Mixed Mice).*

Sixteen mice (17 to 25 grammes) were injected subcutaneously with one milligramme of cobra venom (Walter and Eliza Hall) per kilogram of body weight. Eight of the mice were used as controls (the first group referred to in paragraph 1 above), and eight were injected subcutaneously with 12·5 milligrammes per kilogram of body weight of THA in 0·2 millilitre of solution per 20 grammes of mouse. All of the control mice died and five of the treated mice died. The surviving treated mice were sacrificed on the eighth day. The control mice died in 105 to 233 minutes (average 155 minutes) after injection, while four of the THA-injected mice died in 147 to 220 minutes (average 187 minutes) after injection and the fifth died overnight.

The difference in survival time of the mice that died, 168 and 187 minutes, is not significant statistically, though there is certainly a trend in this direction, and the overnight death, *plus* the survivals, makes the comparative analysis skew. These findings are represented graphically in Figure I, where the interrupted line (open dots) indicates the findings with the controls and the continuous line (open dots) indicates the findings with the treated mice.

The experiment was repeated on 32 "Swiss" mixed mice with Commonwealth Serum Laboratories cobra venom. Sixteen mice (16 to 25 grammes) were injected with 0·7 milligramme of venom per kilogram of body weight subcutaneously and 0·2 millilitre (per 20 grammes) of Tyrode subcutaneously. Sixteen mice (16 to 25 grammes) were injected with 0·7 milligramme of venom per kilogram subcutaneously and 12·5 milligramme of THA per kilogram subcutaneously in a volume of 0·2 millilitre (per 20 grammes) of Tyrode. All the untreated mice died in from 98 to 230 minutes after injection (Figure III, upper line) and 15 of the treated mice died in from 111 to 217 minutes after injection (Figure III, lower line) and one mouse survived.

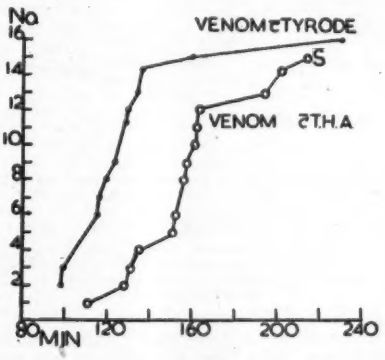


FIGURE III.

Survival times in a series of "Swiss" mixed mice injected with cobra venom. S: survival. Ordinate: number of mice. Abscissa: survival time in minutes. Further details in text.

The average survival time was 127 minutes for the untreated and 159 minutes for the treated mice, though of course the complete survival of one treated mouse could not be represented.

This difference in survival time is highly statistically significant ($P = 0{\cdot}001$ approximately). Of the 24 control mice in this series none survived, while of the 24 treated mice four survived.

### 4. *Effect of Combined Poly-Vinyl-Pyrollidone and Tetra-Hydro-Aminoacridine Therapy on the Mortality and Survival Time of Mice Injected with Venom.*

Sixteen brown mice (17 to 25 grammes) were injected subcutaneously with one milligramme of cobra venom (Walter and Eliza Hall) per kilogram of body weight. Eight of these mice were injected with saline intraperitoneally and used as controls. The remaining eight were injected with 50

milligrammes of PVP in saline intraperitoneally and 12·5 milligrammes per kilogram of THA subcutaneously (0·2 millilitre per 20 grammes of mouse). All the control mice died. Four only of the treated mice died. The remaining four mice were sacrificed on the eighth day. The control mice died in from 100 to 170 minutes (average 132 minutes) after injection of venom. Four of the treated mice died in from 183 to 380 minutes (average 267 minutes) after injection.

These findings are represented graphically in Figure IV, where the left-hand line shows the findings for the untreated, and the right-hand line the findings for the treated mice. Both the difference in survival time in the fatal cases and the reduction in mortality ($P = 0.036$) are statistically significant.

The experiment was repeated with Commonwealth Serum Laboratories cobra venom. Sixteen "Swiss" mixed mice were injected with 0·7 milligramme of venom per kilogram of body weight subcutaneously. Eight of the mice were injected with one millilitre of Tyrode intraperitoneally and 0·2 millilitre of Tyrode subcutaneously and used as controls. Eight of the mice were injected with 35 milligrammes of PVP in polyvidone solution intraperitoneally and 12·5 milligrammes of THA per kilogram in 0·2 millilitre of Tyrode per 20 grammes of animal subcutaneously. All the untreated mice died in from 69 to 118 minutes (average 98 minutes) after injection, and the treated mice, all of which also died, died in from 121 to 230 minutes (average 165 minutes) after injection.

These findings are shown in Figure V, where the left-hand line demonstrates the findings with the untreated, and the right-hand line the findings with the treated mice. It is noteworthy (Figures IV and V) that in both instances

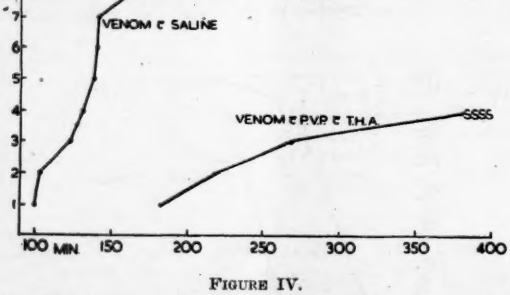


FIGURE IV.

Survival times in a series of "Brown" mice injected with cobra venom. S: survival. Ordinate: number of mice. Abscissa: survival time in minutes. Further details in text.

all the untreated mice died before any deaths occurred among the treated mice. The day of these last experiments (associated with a sudden change in the weather) was very hot and humid, and the presumably increased vascularity of the skin should increase the absorption and local activity of the venom. This probably accounted for the shorter survival times of controls. Modern treatment of snake bite includes local chilling of the part injected.

### 5. *Statistical Analysis.*

Statistical analysis of the Walter and Eliza Hall venom experiments reveals no significant difference in the response of the two strains of mice. There is also no significant difference in the survival time when saline alone is injected subcutaneously. The statistically estimated survival times are as follows: (i) if only venom is given, 149 minutes; (ii) if venom and THA are given (when death occurs), 180 minutes; (iii) if venom and PVP are given, 219 minutes; (iv) if venom, PVP and THA are given (when death occurs), 266 minutes. From the analysis of variance it appears that the PVP and THA act additively on the logarithm of the survival time—that is, there is no synergism.[1]

[1] Assistance in this analysis was given by the Statistics Department, University of Melbourne.

The series was increased with the use of Commonwealth Serum Laboratories venom, which was always injected into "Swiss" mixed mice. The doubtful significance of the increased survival time in the small series that died after receiving THA then became highly significant ($P = 0.001$ approximately). The survivals then appear as in Table I. Each paired group was injected from the same solution of venom, and injections were made alternately into treated and untreated mice individually. This makes each paired group strictly comparable.

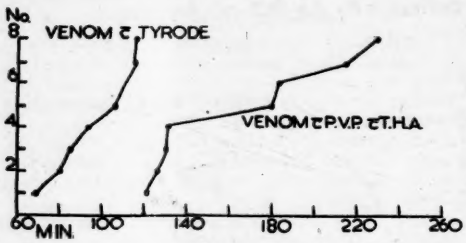


FIGURE V.

Survival times in a series of "Swiss" mixed mice injected with cobra venom. Ordinate: Number of mice. Abscissa: survival time in minutes. Further details in text.

In Table I it is noted that only one of the 64 untreated mice survived, a survival rate of 1·5%, while 11 of 63 treated mice survived, a survival rate of 17·5%. This difference in pooled survival rate is highly significant statistically ($P = 0.002$). Three survivals occurred with the PVP treatment, four with the THA treatment, and four with the PVP *plus* THA treatment, or 13%, 16% and 25% survival rates respectively.

TABLE I.

*Comparison of Survivals in Pooled Treated and Untreated Animals.*

| Breed of Mice. | Proportion of Survivals. | | Treatment. |
|---|---|---|---|
| | Untreated. | Treated. | |
| Swiss mixed .. | 0/8 | 0/8 | PVP. |
| Swiss mixed .. | 1/16 | 3/15 | PVP. |
| Swiss mixed .. | 0/8 | 3/8 | THA. |
| Swiss mixed .. | 0/16 | 1/16 | THA. |
| Swiss mixed .. .. | 0/8 | 0/8 | PVP and THA. |
| Brown .. .. | 0/8 | 4/8 | PVP and THA. |
| Total .. | 1/64 | 11/63 | |

Further, it is to be noted that if the initial shortest survival time in a group of animals was approximately 130 minutes (Figures I, II, III, IV and V), some animals always survived. If the initial death occurred within 100 minutes all the animals died. Once an animal survived when the earliest death occurred at 110 minutes.

The statistical finding that analysis of the variance indicates that PVP and THA act additively and not synergistically is in accord with their markedly different character and presumed different pharmacological actions.

## Discussion.

In this work we have chosen deliberately a dose of venom that is almost uniformly fatal for mice of 20 grammes weight. After doses of 1·0 milligramme of Walter and Eliza Hall venom per kilogram and 0·7 milligramme of Commonwealth Serum Laboratories venom per kilogram only one mouse in a series of 64 animals survived—that is, a mortality of 98·5%. Survival was deemed to have taken place if the animal was alive eight days after injection. In all instances the surviving animals, including those

treated, appeared perfectly well and normal at this time. Of the treated animals, whether given PVP, THA or a combination of the two, 11 mice in a series of 63—that is, 17·5%—survived. This is a highly statistically significant reduction in mortality. Furthermore, in each group treatment with PVP or with THA or with both together significantly increased the survival time in the fatal cases. The longer an animal survives, the longer is the time available for "self" detoxication, and also presumably the longer would be the time available for specific antivenene therapy, or other treatment, to have its effect. Additional measures, such as local chilling of the part injected (the site of the bite), which will delay the noxious enzyme activity of the venom and reduce the level of its impact, and the treatment of shock, may also be expected to be more successful if the expected survival time is prolonged. When it is remembered that whenever the initial death in a series of animals did not occur until 130 minutes after injection, some animals in the series always survived, and further that if the initial death in a series of animals occurred within 100 minutes of injection all the animals invariably died, therapy which prolongs the survival time would appear to be of value. Presumably during this longer period the body is able to deal with a greater amount of venom in its own way and so inherently to improve survival of itself. The value of local chilling of the part in snake bite, now employed quite universally, is undoubted. This procedure probably reduces both the rate of absorption of venom and its local activity to a degree such that the body may be able to cope with what would be otherwise a fatal dose. Tourniquet therapy employs this principle in part, but of course cannot be applied beyond a limited time. Likewise the washing off of venom and incision with sucking out of the poison may reduce the impact of a large dose.

As to the manner in which these drugs prolong the survival time and reduce mortality, we are able only to make tentative suggestions. Poly-vinyl-pyrollidone is a colloid, and as such it might be considered that it could act by adsorbing toxin on to its surface. If this material was then excreted instead of attaching itself to nerve cells and heart muscle cells, mortality might thereby be expected to be reduced. With trypan red, otherwise not so excreted, the suggestion is that PVP adsorbs the dye and the complex is excreted in the urine (Schubert, 1954). Studies with varying colloidal sizes of PVP indicated that the smaller the size of the molecule the more active was the compound in this regard. Schubert suggests that the colloid adsorbs diphtheria toxin so that it cannot enter the heart cells, while tetanus toxin combines inside nerve cells. In our experiments we confined ourselves to the PVP supplied in "Plasmosan", which we had previously found to be of great value in heart perfusions, as judged by the normality of the electrocardiogram (Trethewie and Hodgkinson, 1954). In man PVP could naturally be given intravenously as treatment, as indeed it is in shock, though for other reasons.

The mode of action of THA would appear to be more obscure. In a dose of 1: 100,000 *in vitro*, acetyl-choline synthesis is impaired (de la Lande and Bentley, 1955). This effect might well be produced in mouse nerve tissue after subcutaneous injection of 12·5 milligrammes of THA per kilogram, which we have given. Gautrelet and Corteggiani (1938) showed that cobra venom released acetyl-choline from nerve tissue, and perhaps an impaired synthesis might reduce the release of acetyl-choline one or two hours after injection of venom, since there would then be less available for release. This release of acetyl-choline in nerve tissue of course may play no part in the paralysis of snake venom poisoning. However, a large local release of acetyl-choline at the end-plate might produce neuromuscular block by depolarization, though as yet this mechanism has been ascribed only to anti-cholinesterases. Venom may act similarly on neuronal activity, though as yet few series of neurons in the central nervous system have been regarded as being cholinergic. On the other hand, THA produces inhibition of cholinesterase in the very minute concentration of $1:5 \times 10^6$ (de la Lande and Bentley, 1955). However, our effective dose of THA was much greater than this. It is also not inconceivable that THA may have an effect on the metabolism of neurons. It is described as a mild respiratory stimulant (Bentley, 1952), and this may indicate an effect on central neuron metabolism (perhaps here depressed by venom), or it may indeed act as an antagonist to the respiratory paralysis of the venom, though other respiratory stimulants are not particularly effective in the treatment of snake venom poisoning.


### Summary.

The influence of tetra-hydro-aminoacridine and poly-vinyl-pyrollidone on the survival time and mortality in mice following the injection of cobra venom (*Naja Naja*) has been investigated.

The survival time is significantly prolonged under these circumstances. When the two drugs are given concurrently to mice there is an additive non-synergistic effect on the survival time.

The survival rate of all animals injected with PVP, THA and a combination of the two is increased statistically with high significance when compared with controls.

The possible mechanism of these activities is outlined.


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## ORANGE JUICE AND DIGESTIVE DYSFUNCTION.


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IT has been observed that certain individuals are distressed after the consumption of orange juice, and that in most of these cases there seems to be a relation to liver function. The effect often appears to be correlated with histories of frequent bilious or gall-bladder attacks or follows cholecystectomy, and has also been recorded during sea-sickness, jaundice and migraine or after over-indulgence in alcohol. In most instances distress is only noticed, or is accentuated, during an attack of any of the disorders mentioned, with reasonable tolerance to the juice in the intervening periods.

Symptoms are variable, ranging from numbness of the lips and surrounding areas to nausea, "heartburn", gastric

pain, vomiting, diarrhœa and headache; the majority of these symptoms usually occur within one-quarter to half an hour after consumption of the juice. The effect appears to be different from the allergic reactions manifested in eczematous children. Joslin and Bradley (1951) have shown the peel oil to be the causative factor in these cases.

### Historical Survey.

Alvarez and Hinshaw (1935), in a study of food idiosyncrasies in 500 patients, found symptoms similar to those cited above. They recorded the cases of patients who became sensitive to certain foods after cholecystectomy, and this finding also has been confirmed at the Royal Melbourne Hospital, where it has been noted that a number of such patients have become sensitive to orange juice. Alvarez (1934) also cited the cases of four patients with "pseudocholecystitis" who were unimproved by cholecystectomy, but obtained complete relief of symptoms when certain foodstuffs were omitted from the diet. Jaundice occurred in at least two of these patients, and Alvarez postulated that food idiosyncrasy must in some way affect bile secretion. It is conceivable that this type of reaction may occur in the cases in which orange juice causes distress.

The fraction of the orange juice responsible for the disturbance in humans is unknown; however, it is generally believed that it may be due to small quantities of peel oil expressed during collection of the juice. Observations by dietitians on the other hand have led to the belief that the causative factor is in the juice itself.

A study of the literature reveals very little of relevance to the whole juice of the orange. However, work by Eberhard and Bower (1940), by Clayfor, Smith and Turner (1941), and by Haggard and Greenberg (1941) shows that fruit juices have an effect of stimulating high, free, gastric acidity, an effect which occurs only in the early stages of digestion. The acids in the fruit juice were presumed to be responsible. Sobotka (1937) made the following statement:

> Many substances stimulating gastric, pancreatic and duodenal secretion will cause the liberation of substances which in turn, when resorbed, act directly as cholagogues.

Thus the increased acidity caused by the juice could cause increased biliary secretion. This theory would appear to be negated by the fact that lemon juice, of considerably lower pH, and containing similar organic acids to those present in orange juice, is well tolerated by individuals sensitive to the latter.

The work of Yonemura (1926), Sugano (1927), and Murakami (1928) suggests that vitamin *A* stimulates bile flow. In 1952, Natajaran and Mackinney demonstrated the presence in orange juice of $\beta$-carotene, a vitamin *A* precursor. It thus seemed possible that the effect on the bile was due to the $\beta$-carotene or other pigments of the orange juice. This possibility was further supported by the difference in pigmentation of the orange and the lemon, and the fact that other orange-red fruits, such as tomato, may cause biliousness in certain subjects.

### Experimental Investigations.

Preliminary work was concentrated on an attempt to find a suitable laboratory animal, which could be used to assay the effect of fractions isolated from orange juice. It was postulated that, if the effect was related to bile secretion, when a choleretic material was fed there should be a decrease in the fæcal fat, accompanied by an increase in the rate of fat absorption.

Rats were selected as experimental animals for the purpose of the investigation. They are of useful size for housing and handling in metabolism cage studies and of omnivorous habit, and since these animals do not have gall-bladders, more direct response may be expected to stimulants of bile secretion. The rats were fed upon weighed diets of constant fat level, supplemented for different groups with orange juice, lemon juice, cholic acid or a mixture of the organic acids usually present in orange juice. By the use of the method of Van de Kamer, Bokkel Huinink and Weyers (1949), five-day fæcal fat balances were studied both during a control period and during the juice-feeding period. The fluctuations of fæcal fat and of total fat absorbed between groups fed the different supplements were not sufficient to enable this method to be used for assay work for the purposes of this study.

However, it was interesting to note that the animals fed the choleretic material cholic acid developed considerable decreases in their fæcal fat and increased fat absorption. The results also suggested that lemon juice might exert an inhibitory effect upon fat absorption. That this was not solely due to the low pH of 2·2 was shown by a slight increase in fat absorption when animals were given an organic acid mixture comparable in composition and pH value to lemon juice.

Since we had failed to find a suitable laboratory animal for such assay it was necessary to resort to the use of human volunteers for testing the samples or fractions isolated.

### Collection of Juice.

The juice of navel oranges, purchased on the open market, was obtained by the usual household method of hand extraction, which does not unduly bruise the albedo. The juice was then placed in a Waring Blendor for one minute in order to break up the pulp cells and to allow more ready extraction of the contained fractions.

### Separation of Fractions.

The juice was extracted for twenty-four hours with a mixture of equal parts of ethanol and petroleum ether. This left the residual juice almost colourless. The alcohol-ether extract was then dried under reduced pressure at approximately 18° C., and the orange-yellow mixture was dissolved in glycerol. To this last had been added a mixture of citric and malic acids to give a final concentration of 1% citric and 0·1% malic acid.

Doses of this extract, approximately equivalent to the quantity obtained from one orange, were given to two test subjects and also to three others known to tolerate oranges well. Control doses of the glycerol-acid solution and of the residual juice were also given. To eliminate the effect of psychic factors, the subjects were given the samples in bottles labelled only by a symbol, without comment as to derivation or possible reaction. The tests were made approximately two hours after consumption of the patients' normal breakfast, which was assumed to have no component which might interfere with the reaction. The results are summarized in Table I.

TABLE I.

*Effect of Alcohol Ether Extract of Orange Juice on Test Subjects.*

| Subject. | Solution Tested. | | |
|---|---|---|---|
| | Glycerol-Acid Solution (Control). | Glycerol-Acid Solution of Extract. | Residual Juice (Control). |
| $T_1$ | No effect. | Nausea and headache within half an hour. | No effect. |
| $T_2$ | No effect. | Nausea and numbness around mouth. | No effect. |
| $C_1$ | Some nausea. | Some nausea. | No effect. |
| $C_2$ | No effect. | No effect. | No effect. |
| $C_3$ | No effect. | No effect. | No effect. |

The results obtained suggested that the fraction being sought was soluble in organic solvents and was probably therefore a pigment or flavouring constituent. To obtain a further fractionation the steam-volatile components of the whole juice were collected and tested on human subjects. This fraction was oily and had a distinctly "orangy" odour, together with a sharp "musty" odour. The flavour was distinctly "orangy" and remained in the mouth for some time, which is typical of the classical bitter component of tastes. The residual juice was bitter with little orange flavour. Tests were carried out as before, the test solutions were sweetened with sucrose,

and sucrose solution was used as a control. The results are summarized in Table II.

These results showed quite definitely that the active principle being sought was in the steam-volatile fraction of the juice and thus was probably a flavouring agent.

Further tests were carried out on the steam-volatile fraction of carefully extracted pith-free juice and also of the pithy tissue. These tests revealed that the active principle was present in the volatile flavouring portion of pure juice and that the bitterness and musty flavour were derived from the pithy portions. A sample of pure peel oil obtained from the Museum of Applied Arts and Sciences, Sydney, did not cause discomfort in any of the test subjects. With the aim of eliminating psychological

TABLE II.

*Effect of Volatile Fraction of Orange Juice on Test Subjects.*

| Subject. | Solution Tested. | | |
|---|---|---|---|
| | Sucrose Control. | Distillate and Sucrose. | Residual Juice and Sucrose. |
| $T_1$ | No effect. | Violent headache within half an hour. | No effect. |
| $T_2$ | No effect. | Nausea immediately. Headache within half an hour. | No effect. |
| $T_3$ | No effect. | Abdominal pain within one hour. | No effect. |
| $T_4$ | Nausea. | Dry retching within half an hour. | No effect. |
| $C_1$ | No effect. | No effect. | No effect. |
| $C_2$ | No effect. | No effect. | No effect. |
| $C_3$ | No effect. | No effect. | No effect. |
| $C_4$ | No effect. | No effect. | No effect. |

errors more completely, further tests were carried out on the fractions at various stages of distillation, one sensitive test subject and one insensitive normal subject being used. The results are summarized in Table III.

These results confirm the finding that the factor responsible for the disturbances due to orange juice is found in the steam-volatile fraction of pure juice.

TABLE III.

*Effect of Various Fractions on Two Subjects.*

| Fraction Tested. | Test Subject. | Control Subject. |
|---|---|---|
| (i) Whole orange juice, 90 millilitres. | Violent headache within 15 minutes. | No effect. |
| (ii) Petroleum ether, alcohol extract dissolved in glycerol-acid mixture (glycerol *plus* citric acid 1% *plus* malic acid 0·1%). | Some nausea. | Unpleasant taste—no effect. |
| (iii) Volatile fraction of pure juice, distilled at 75° C. and 300 millimetres pressure. | Violent headache within 15 minutes. | No effect. |
| (iv) Residue from (iii) diluted to original volume with water. | No effect. | No effect. |
| (v) Volatile fraction, first 15 millilitres distilled from 270 millilitres of juice; removed at 50° C. | Violent headache within 15 minutes. | No effect. |

Owing to difficulties in obtaining volunteers it was impossible to continue with further work in this direction. An attempt was then made to determine the nature of the material. Hall and Wilson (1925) analysed the steam-volatile components of orange juice and found them to comprise less than 0·1% of the total volume of the juice. Ethanol, acetone, acetaldehyde and formic acid were found, all of which are soluble in water, together with a group less soluble and extracted by ether. This latter group comprised an olefine alcohol, $C_{10}H_{18}O$, related to, but not identical with, linaloöl, isoamyl alcohol, phenyl ethyl alcohol, esters of formic, acetic, and caprylic acid, and probably the terpenes geraniol and terpineol.

Our experiments suggest that the material being sought is amongst the second group mentioned. Further tests on the material isolated have demonstrated the presence of unsaturated links, aldehyde, and/or keto groups, an absorption peak in the ultra-violet region at 244m$\mu$, and a freezing point below –12° C. This indicates the presence in the fraction of organic molecules of a structure consistent with that of the terpenes, reported present in the steam distillate of orange juice. Prevost and Binet (1888) suggested that certain terpenes, including terpineol, have choleretic properties.

## Conclusions.

From the findings reported in this paper it can be concluded that an active principle amongst the highly volatile flavouring constituents of orange juice is responsible for the digestive and other disturbances produced in certain individuals after consumption of this foodstuff.

This principle is not one of the pigments normally present in the fresh juice; but the possibility of a degradation product of $\beta$-carotene, such as $\beta$-ionine, or other pigments with such activity, cannot be excluded.

It must also be noted that the oranges used for this experiment were of the navel variety, known to contain additional flavouring constituents, such as indole, not present in other types of oranges.

The findings do suggest that the terpenes, recorded as being normally present in orange juice, may prove to be the causative factors.

Whether or not the reaction produced is due to a choleretic effect was not proven.

## Summary.

An attempt was made to determine the fraction responsible for the distress caused in certain individuals after the consumption of orange juice.

The active principle was found to be present in the steam-volatile fraction of the juice and not in the pith, as originally believed.

It is suggested that the substance is a readily volatile organic molecule, possibly a terpene, present in small amounts, but of considerable potency.

For practical purposes the removal of this fraction would present certain difficulties, since the major flavouring constituents of orange juice are all volatile, and the residual material is tasteless and unappetizing.

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## A FURTHER NOTE ON THE POSSIBILITY OF INDUCING ATROPHY OF THE HYPERTROPHIED PROSTATE GLAND BY CUTTING ITS BLOOD SUPPLY.

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IN 1954 the writer put forward as a surgical suggestion the possibility of inducing atrophy of the hypertrophied prostate gland by cutting its blood supply (Craig, 1954).

This suggestion arose from two series of observations: firstly, the well-known clinical fact that, in the absence of infection, the body can absorb large quantities of dead tissue, and secondly, the results of the researches into the blood supply of the prostate made by Flocks (1937). The following paragraph, taken from Flock's article, is the key to the whole project:

> The course of the urethral arteries to the lateral lobe in bilateral hypertrophy and the amount of tissue supplied by them is beautifully demonstrated in those cases where before the arteries were injected a ligature was placed on the right side at the internal urethral orifice at 11 o'clock so as to include a piece of tissue 2 mm. in diameter. After the injection and clearing a marked difference is to be noted between the two sides. The side with a ligature shows a tremendous interference with the blood supply to the lateral lobe. In fact if the suture had caught just a little more tissue so as to include one vessel placed more deeply the entire lateral lobe would have been practically avascular. On the other hand the side without the ligature shows a profuse blood supply entering at the prostatic-vesical junction and coursing distally through the substance of the lateral lobe—i.e. the urethral group of arteries.

The writer described the attempts made by him to interrupt the blood supply of the hypertrophied prostate. These fell into three anatomical phases. In the first he separated the prostate from its capsule in those areas where it was presumed that the arteries entered. Although there may have been partial success in one of the cases in which this was tried, it was decided that the operation was unsound, inasmuch as devitalized tissue was exposed to the irritating and possibly infected urine. In the second phase attempts were made to place sutures round the arteries just before they entered the bladder. On none of these occasions did the writer feel certain of his anatomical whereabouts. In the third phase he, on one occasion only, tied that part of the right internal iliac artery which gave rise to the pelvic arteries. Three weeks after this operation, which was performed in conjunction with cystostomy, he opened the bladder again and felt certain that the hypertrophied lobe on the side of the sutured artery had shrunk considerably. It struck the writer very forcibly at that time that if the desired interruption to the blood supply of the prostate gland could be brought about by tying both internal iliac arteries, it would be an extremely easy operation to perform. He considered, however, that it might be a dangerous procedure, inasmuch as the blood supply to the rectum could be cut at the same time. He thought, however, that should it ever be shown that ligature of both internal iliac arteries was without danger, this procedure should be the next line of investigation. At this stage he was obliged to give up surgery and therefore went no further into the matter.

The purpose of this note is to point out that it has now been demonstrated—by Henry Mortensen, of Melbourne—that both internal iliac arteries can be safely ligated. The following is a letter addressed by him to fellow members of the "Urological Correspondence Club"; it is dated January 8, 1956:

> S.W.T., aged 69, was operated upon by transurethral resection for relief of gross bladder neck obstruction. The operation was regarded as a perfectly satisfactory one and the patient had clear drainage from his catheter for seventy-two hours. He then had a sharp secondary hemorrhage which required evacuation of the bladder but ceased quickly. This was repeated three days later and again at intervals of similar duration, until after a period of fourteen days after operation he bled through his catheter and around it a matter of three pints in a very few minutes. After transfusion his bladder was opened and when soft clot was cleared away from his prostatic cavity two huge vessels of a calibre never previously seen in prostatic surgery were noted deep down in the prostatic cavity at six o'clock and eight o'clock on the clockface. Ligature of these vessels was undertaken with difficulty because of the friable nature of the tissue involved. Further, because of the completeness of the resection the proximity of the rectum made the taking of a large bite fraught with considerable danger. However, the cavity having been packed with Gelfoam, the patient was returned to the ward with a blood pressure of 120 and with the bleeding almost completely ceased. This procedure was successful for forty minutes, when he began to pour again. He was returned to the theatre and the internal iliac arteries on both sides were tied. This stopped the bleeding, and today, seven days after the procedure, the drainage is quite clear. In the first operation for the exposure of the bladder, when the peritoneum was being stripped back a hard mass was felt which on first thought appeared to be a tumour of the bladder but subsequently was determined to be of bowel origin. At the second procedure for the tying of the vessels this was proved to be a carcinoma of the sigmoid colon, no symptoms of which had been elicited in his original history.
>
> This case is brought to the attention of members because it is felt that the tying of the internal iliac arteries is a procedure which can be done without risk to the patient under such circumstances as have been described in gross uncontrollable primary and secondary hæmorrhage. It is used also in our practice as a routine in the operation of total cystectomy and in that procedure the amount of blood loss is reduced very considerably.

Now that this demonstration has been made, the writer feels that further investigation into the possibility of cutting the blood supply to the hypertrophied prostate gland and thus inducing its atrophy by tying the internal iliac arteries could well be undertaken.

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## "ACUTE ONSET" MANIFESTATIONS OF CHRONIC DISEASES: A SHORT DIAGNOSTIC STUDY.

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CHRONIC DISEASES usually start insidiously. Slight, vague, evanescent symptoms keep coming and going; in the beginning they are hardly noticed and not heeded at all. But as time advances they manifest themselves more often and increase in intensity. The disease generally takes a slow and protracted course; it may go on for years

with phases of activity and quiescence. It may be that for a while the patient appears symptomless or that the disease remains in a more or less stationary form, and then the patient grows worse again. In the great majority of the cases the patient progressively improves and eventually is cured. In other cases his condition deteriorates and he dies.

In the course of such a chronic disease, however, sudden acute manifestations may occur at any time, the "acute complications" of the chronic disease. They come unexpectedly, often at a time when the patient seems better. These acute manifestations appear in every possible form, are mostly of serious nature and are therefore of prime importance. They may immensely accelerate the original course of the disease, they may represent an imminent danger to life, and indeed they may often bring about death. The new manifestation may be of short duration or may be of long standing; often it heralds the onset of a second chronic disease, from which the patient has to suffer incomparably more than from his primary disease.

These acute manifestations often occur in every field of medicine, are well known, and are dealt with in considerable detail in the text-books. The following are examples. A patient with gastric or duodenal ulcer has suffered from slight or severe pain over the last year. Suddenly he becomes off colour, feels faint or collapses, and vomits a large quantity of dark red blood, or else his bowels move and he passes a big mass of tarry stool. This patient has suffered a hæmorrhage. Another patient with the same complaints suddenly experiences excruciating pain in the upper part of the abdomen; the pain goes on for hours, he may vomit, and the abdominal walls become progressively harder; the ulcer has perforated. A man in his early fifties, who has more easily grown tired on strenuous work over the last months than before, who gets a headache if he is tired, or who has felt light tightness in the chest on exertion for some time, suddenly gets very severe pain behind the sternum, which lasts for hours and necessitates the injection of morphine. It is obvious that he has slowly progressive hardening of the arteries and has suddenly had a heart attack, a coronary occlusion. A woman with the same slight complaints suddenly has a dizzy spell and some minutes later develops weakness or paralysis of one side with transient impairment of consciousness. She has had a stroke, hæmorrhage in the brain or obstruction of an artery. A patient with long-standing hypertension suddenly has an attack of severe vertigo with vomiting; another with the same disease gets an attack of pulmonary œdema precipitated by an emotional upheaval. A patient with tuberculosis of the lungs may suddenly have a severe hæmorrhage; another in the same sanatorium abruptly suffers from intense pain in the right side of the chest with dyspnœa; she has developed a pneumothorax. Sudden death may occur in patients who have been suffering from anginal pain for a long time or from congestive heart failure. I could enumerate a long series of such acute manifestations in the course of a chronic disease, of the existence of which both patient and doctor have known for a long time.

But every doctor has been taught, and knows well from his own practice, that such acute manifestations may appear in a seemingly healthy person as the first symptom of a completely unsuspected condition or a chronic disease. They come all of a sudden, like a bolt from the blue, and are highly surprising to the patient and mostly to his doctor as well. All the above-described acute symptoms, and all those to which I have just referred, may appear in the form of an "acute onset" of an illness which has been completely silent until that time. The occurrence of these symptoms in this form is very much rarer than their occurrence in the course of a known chronic disease, but they are, of course, all of the same importance.

It is a well-known saying that one of the seven sins of medicine is hunting for rarities. I hasten to state that a large proportion of these "acute onsets" which I am discussing here are not rare at all; but at the same time I hasten to emphasize a qualification at this point. In a large number of these cases the person who was seemingly healthy until that time was not completely free of symptoms. Detailed interrogation reveals now that the patient has already had one or other symptom during the last months or years, but the symptoms were so mild, disturbed him so little, and interfered so little with his everyday activity that he neglected and ignored them completely, repressed and concealed them, and did not find it necessary to consult his doctor because of them. But the doctor well recognizes now in retrospect that these were the premonitory symptoms of a smouldering chronic disease which suddenly erupted in a violent attack. A regular periodical medical check-up would surely reduce the "surprise" of these "acute onset" manifestations to a large extent.

But in spite of all this I must point out that acute onset manifestations are not particularly rare in diseases which indeed have not produced any symptoms whatever in the past. It is important to draw attention to this; I feel sure that it is well worth while and instructive to deal with the subject. It may help to avoid pitfalls in the making of the right diagnosis. So I will review some of these "acute onset" symptoms. I have collected most of them from the literature, but I have seen many of them in my own clinical practice.

Massive hæmorrhage (vomiting of blood) may occur abruptly in a person who has not felt the slightest symptom of a gastric or duodenal ulcer. Hæmorrhage was the first sign or symptom of ulcer in 41 of 311 patients with proven ulcers admitted to hospital because of hæmorrhage (Morrow, 1955). In most recent times it has been pointed out that severe hæmorrhage or perforation may be the first symptom of a latent duodenal ulcer during protracted cortisone therapy. Occasionally massive hæmorrhage is the first symptom of duodenal diverticulum that has been absolutely silent until that time; and in the same way massive hæmorrhage may suddenly appear in patients with post-necrotic cirrhosis who have been unaware of their disease and have seemed to be enjoying normal health (Ingelfinger, 1955).

As I mentioned above, perforation may be the first manifestation of a duodenal ulcer.

I remember well the case of a young tram conductor—he may have been in his early twenties—who was admitted one morning to the Internal Clinic of Budapest with the typical early signs of perforation of an ulcer. On being questioned, he emphatically repeated that he had never had the slightest gastric disturbance. He had driven his tram about an hour earlier just past the Clinic, when quite suddenly he felt a sensation "as if a knife had been pushed in his upper abdomen". He was hardly able to drive the tram to the nearby terminus, and then he collapsed. Operation was performed immediately and revealed a perforation in the duodenum the size of a pinhead, with minimal induration of the ulcus basis.

I have seen one or two people who suddenly developed aphasia or slight hemiparesis without any premonitory symptoms in the past. On inquiry some of them confessed that they had received antisyphilitic treatment twenty years or so earlier; others denied any venereal disease, but the blood test for syphilis gave a positive result. Syphilis was formerly very often the cause of such startling acute onset manifestations. A severe gastric crisis was often the first symptom of latent tabes; according to Nuzum (quoted by Henning, 1954) this occurred in 17% of cases. It might mimic an acute abdominal emergency, and many such patients were operated on. I remember the saying of a German surgeon, that for him the discovery of unequal pupils which did not react to light in a patient already lying on the operating table was always a most dramatic moment.

One of the most interesting cases in this group was that of a man in his early fifties who developed sudden confusion with partial loss of memory when he read about the declaration of the first World War on his holidays at the seaside. He had practically never been ill before. In an attempt to return immediately to Budapest he entered the wrong train and had to be picked up by his son somewhere in Austria, when he presented the picture of fully developed paresis of the insane.

A man in his forties was under my care in the military hospital in Budapest about the end of the first World War; he had been admitted to the hospital because of tropical malaria acquired in Albania. He said that he had never been ill before, in spite of the fact that he was already in the fourth year of his military service. He was convalescent and without a rise in temperature for a couple of days. During a ward round I had just passed his corner when suddenly I heard him coughing violently. Turning towards him I saw the gush of an immense quantity of fresh red blood streaming from his mouth. For a moment the whole staff stared frozen at the horrible picture. Then we ran to his bed, but were unable to be of any help to him; he bled to death within a few minutes. The necropsy revealed an aneurysm of the thoracic aorta the size of a small apple which had perforated in the left main bronchus.

A woman in her forties, during a game of cards, suddenly had a dizzy spell and became paralysed on her right side some minutes later. She had a completely silent mitral stenosis and evidently had an embolus coming from the left auricle into the brain.

Let me repeat that I could enumerate a long series of such surprising "acute onset" manifestations of a chronic disease which had hitherto been unknown and silent. We must always keep in mind that any acute onset of a startling symptom complex — no matter whether mild or severe — may originate from a hitherto totally symptomless chronic disease. I would go even further and point out that, with the exception of acute infectious diseases, acute appendicitis and a couple of other acute diseases, surprising acute onset manifestations of a disease much more often than not originate from a chronic disease. Let us consider some more of them.

In a paper on myocardial infarction Maurice *et alii* (1955) report a study of 108 patients with myocardial infarction; they found that 60·2% had had the classical form with no premonitory symptoms.

Renal colic or a compression fracture may be the first symptom of latent hyperthyroidism. A spontaneous fracture may be the first symptom of far-advanced osteoporosis. A large number of patients have been operated on because of severe acute abdominal symptoms; the surgeon has been unable to find any abnormality, and the cause has been unsuspected chronic porphyria. According to Waldenström (quoted by Henning, 1954), until 1937, 40% of patients with porphyria were operated on because of a seemingly acute abdominal emergency. Very severe abdominal colicky pains may be the first manifestation of silent chronic lead poisoning. A patient presents symptoms of acute pneumonia; the course of his illness shows that he is suffering from lung cancer. A patient undergoes an abdominal operation because of seemingly acute severe gall-bladder colic, which has been initiated by a crisis of a so far unknown hæmolytic icterus. Many patients undergo operations, whose sudden acute abdominal symptoms have been caused by a posterior cardiac infarct, although until that time there has been not the slightest sign of any cardiac disturbance. The same happens with patients who develop a sudden dissecting aneurysm with prevailing abdominal symptoms. Not uncommon is the acute abdominal catastrophe caused by twisting of an unidentified ovarian cyst. Acute intestinal obstruction may exceptionally be caused by cancer of the sigmoid which has produced hardly any symptoms or even no symptoms at all until that time. The statistics reveal that a larger number of sudden acute intestinal obstructions are caused by symptomless chronic conditions or diseases (strangulation caused by peritoneal adhesions or bands *et cetera*) than by real acute conditions (volvulus, intussusception, strangulation of internal hernias).

In the literature I have found accounts of unusual and indeed highly surprising acute onset manifestations of a silent chronic disease — for example, an acute crisis in unsuspected Addison's disease or acute severe abdominal symptoms in latent tetany. In some cases the first manifestation of *arteriosclerosis obliterans* is severe, extensive, sudden arterial occlusion (Allen *et alii*, 1946). I have found a description of sudden hemiplegia caused by hæmorrhage in a completely silent cerebral metastasis from a symptomless small cancer of the stomach.

One of the most startling acute onset manifestations of a chronic disease in my experience was that of a man in his sixties who developed almost complete paraplegia within twenty-four hours. Over the last three months he had felt just a little tired. The X-ray examination gave evidence of innumerable deposits in the bones from an absolutely symptomless cancer of the prostate; the first lumbar vertebra was found completely collapsed.

The most formidable and tragic acute onset manifestation of an unsuspected chronic disease is sudden death occurring unexpectedly within some minutes. A man or a woman drops dead on the street, in the theatre or at home, or is found dead in bed in the morning. The wife or husband, the relatives, the friends declare that they have never heard any complaints whatever from the deceased prior to the tragic end. This kind of sudden death is mostly caused by coronary occlusion on the basis of symptomless coronary sclerosis. It is not a very rare event, but of course it is very much rarer than the sudden death of an individual who has already shown some signs of his coronary disease. Much rarer are unexpected deaths from a fulminating hæmorrhage in the brain, from massive embolism in an artery of the brain, or from *status thymicolymphaticus* in individuals without any premonitory symptoms.

### Summary.

"Acute onset" manifestations are not rarely the first symptom of a previously completely silent disease.

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## KORSAKOFF'S DISEASE DUE TO LEAD AND ARSENIC POISONING.

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THE accepted diagnostic symptoms and signs of Korsakoff's disease are as follows: a history of alcoholism, peripheral neuritis, a loss of memory associated with undue suggestibility and confabulations of memory. The onset may be acute; in this case the prognosis may be relatively good. More often, however, the onset is slow and insidious, and the prognosis is then poor.

It is also accepted that the disease may be due to lead and arsenic poisoning. However, in actual practice this condition has been so rarely diagnosed that one is apt to overlook its possibility in a differential diagnosis.

This article has been prompted by three cases of Korsakoff's syndrome due to lead and arsenic poisoning occurring at the Hydebrae Private Hospital, Strathfield, during the past four years. The hospital specializes in the treatment of alcoholics and has treated well over 1000. Only a small minority of these patients have shown Korsakoff's disease. The fact that three of them had lead and arsenic poisoning shows that the condition must be much more common than is generally believed.

Patients with Korsakoff's disease due to alcoholism run an even clinical course. Even if the symptoms are acute on the patient's admission to hospital they quickly settle down. Acute exacerbations do not occur, and in the vast majority of cases the restlessness disappears within a fortnight.

In the three cases under review the restlessness persisted for weeks and acute exacerbations of symptoms occurred more than once. Even the peripheral neuritis was atypical. In acute alcoholics the calves of the legs are chiefly affected; in chronic cases there is a general muscular wasting of the legs. Nevertheless the patients seem to be able to move about, and they complain little of pain. However, the patients in the present series complained bitterly of pain in the upper part of their legs, and there was definite non-coordination of movement, with a tendency to fall against walls.

Lead and arsenic occur normally in the urine. The upper limit of excretion of both is 0·1 milligramme per litre of urine. In the three cases the amounts were well above the upper limits of normality. In one the lead reading was 0·37 milligramme per litre. Without any special treatment the readings in all cases gradually returned to normal.

The patients were women in middle life, with a history of taking alcohol to excess. On the face of it, on their admission to hospital all were suffering from acute alcoholism. Only a highly concentrated experience of alcoholics in a special hospital made us suspect a diagnosis other than alcoholism.

One made a complete recovery; one became a hopeless dement; the third, although superficially well, remains somewhat vague and indecisive mentally.

The cases were reported to the police, who did not reveal their conclusions as to the origin of the poisoning.

These cases would indicate that many cases of lead and arsenic poisoning must remain undiagnosed. This must be more so today, when restlessness is too apt to be treated with electroconvulsive therapy. This confuses the patients and masks the true symptoms of the causative disease.

Toxic psychoses are but symptoms of bodily disease. Treatment should be directed at the causative disease and not *per se* at the mental symptoms. For this reason I am firmly of the opinion that shock treatment is contra-indicated in alcoholism.

These cases further indicate that exact diagnosis is still essential in psychiatry. This point is apt to be lost sight of in the present craze for shock treatments and for the esoteric — and to me the somewhat incomprehensible — language of present-day psychiatry.

## CAUDAL ANALGESIA IN LABOUR WARD PROCEDURES: A SERIES OF THREE HUNDRED CONSECUTIVE CASES.

By J. MAURICE BARRETT, M.B., B.S., D.G.O., M.R.C.O.G.,
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AT the Royal Women's Hospital, Melbourne, caudal analgesia has been widely used for both obstetrical and gynæcological procedures. Approximately 1500 patients per year have received caudal analgesia administered by the members of the anæsthetic and resident medical staff. For the purposes of this paper the observations on a consecutive series of 300 patients who received caudal analgesia during labour ward procedures were accurately documented over a period of five months. The majority of these procedures were performed by the members of the resident medical staff, who learned both the anatomy concerned and the technique involved during the term of their appointment at the hospital.

### Procedures in which Caudal Analgesia may be Used.

#### *Repair of Episiotomy.*

At the Royal Women's Hospital many of the normal deliveries are carried out by medical students and members of the nursing staff. In many cases an episiotomy is required at the time of the delivery. The episiotomy is repaired by a member of the resident medical staff after the completion of the third stage of labour. The opportunity is taken to become expert in the technique of caudal analgesia by the practice of this procedure in the repair of the tissues. At the same time there is not the distortion or distension of the tissue planes which accompanies a repair in which local infiltration anæsthesia is used.

#### *Delivery by Forceps of the Fœtal Head in Vertex Presentations.*

Caudal analgesia was used in head on perineum, low pelvic and mid-pelvic forceps applications. Manual rotation of the occiput to the anterior position was performed in many cases, and frequently an episiotomy was necessary to complete the delivery. Once satisfactory analgesia had been obtained, the delivery of the baby was carried out without that apprehension on the part of the obstetrician which is often present when a general anæsthetic has been administered, especially when that anæsthetic has been given by inexperienced personnel. This important fact applies particularly when forceps delivery is indicated in a patient who has recently had a meal, or in a case of prolonged labour when the risk of vomiting during the induction of general anæsthesia is always present.

Another advantage of caudal analgesia in this type of delivery is the maintenance of some tone in the uterine and anterior abdominal wall musculature. Under these conditions there is little prospect of disimpacting the fœtal head so high above the pelvic brim that forceps application becomes very difficult or even impossible. During manual rotation of the occiput to the anterior position, suprapubic pressure and other assisting manipulations can be performed without any distress to the mother. When we consider that the complications of general anæsthesia play a considerable part in maternal morbidity and mortality, the advantages of caudal analgesia become quite obvious. The problems of dealing with the effects of prolonged anæsthesia on the fœtus are also eradicated.

#### *Manual Removal of the Retained and Adherent Placentæ.*

In such a large series of cases the complications of retained and adherent placentæ naturally did arise. Manual exploration of the uterus and removal of the placenta was carried out without any distress to the patient, and there was no evidence of shock produced by this procedure. No difficulty was experienced in dilating the reformed cervix in cases in which that factor was encountered.

The complications of cervical laceration and perforation of the uterus did not arise, nor was there any increase in post-partum hæmorrhage, shock or maternal morbidity. The response to injection of ergometrine by the intravenous route was not impaired.

#### *Management of Delivery in Twin Pregnancy.*

Twin pregnancy is often complicated by the presence of preeclampsia. In such cases, when the first fœtus presents by the vertex, forceps delivery is carried out when the presenting part comes on view. Caudal analgesia was used under such circumstances on three occasions. In each case the second fœtus also presented by the vertex and was also delivered by forceps extraction without additional anæsthesia.

### Anatomy and Physiology Involved.

Caudal analgesia is a form of regional nerve block in which insensibility to pain is produced by the injection of a local anæsthetic drug into the sacral canal via the sacral hiatus. The injection is extradural and makes use of the peridural space which exists in the lumbar, thoracic and cervical regions, lateral and posterior to the dura. In more than 99% of cases the dura closes about the *filum terminale* not lower than the level of the second sacral foramen, so that the distal part of the sacral canal is occupied only by the peridural space and its contents —that is, nerves, loose areolar connective tissue, fat, lym-

phatics and blood vessels. Below the closure of the dura the sacral canal gives passage to the third, fourth and fifth sacral and coccygeal nerves and their dorsal root ganglia. The veins tend to lie in a plexus on the anterior wall of the canal.

It has been shown that the level reached by fluid injected into the sacral canal through the sacral hiatus is dependent to a great extent on the volume of fluid employed at injection, on the rapidity of the injection, and on the use of gravity by posture. Of great importance is the fact that not only are somatic trunks affected, but also the sacral parasympathetic nerves are blocked. Blocking of the sacral nerve roots abolishes the pain resulting from distension of the birth canal, paralyses the skeletal musculature of the perineum, and abolishes tone in the smooth muscle of the cervix. Extension of the block to include the eleventh thoracic root abolishes the pain of uterine contractions without impairing their force. Extending the block to the sixth thoracic segment may impair the strength of the uterine contractions.

### Technique of the Injection.

The patient is placed in the left lateral position along the right side of the bed, and with her thighs and knees flexed. She should be informed that she is to receive an injection in the lower part of her back, and that the injection will relieve her pain and allow the delivery of her baby. The presence of a reassuring nurse is of great assistance to the patient.

All apparatus used in carrying out the injection must be sterilized by autoclave and comprises the following: (i) one syringe of capacity two cubic centimetres with two hypodermic needles one inch in length; (ii) one syringe of capacity 20 cubic centimetres with Luer-Lok connexion, and two 20 gauge needles two inches in length; (iii) the anæsthetic agent in a sterile container; (iv) one 20 cubic centimetre ampoule of normal saline; (v) sterile swabs; (vi) an antiseptic solution, such as "Zephiran" one in 1600 in alcoholic solution; (vii) Gallipots for mixing solutions.

The presence of strict asepsis must be stressed. The skin over the lumbar, sacral and coccygeal areas and of the buttocks is prepared under strict antiseptic conditions, and the hands and forearms of the anæsthetist are prepared as for any surgical procedure. The sacral hiatus is then identified by palpation. The hiatus is always above the gluteal fold. Palpation from above downwards along the posterior aspect of the sacrum will exclude the presence of an occult *spina bifida*. The sacral hiatus is usually central in position, and lies one finger's breadth above the upper limit of the gluteal fold. Another method of identification of the sacral hiatus is to locate the tip of the coccyx, and then to palpate at a level two fingers' breadth above that bony landmark. The sacral hiatus is then identified by the presence of the cornuæ. It is covered by the firm sacro-coccygeal membrane. Once the sacral hiatus is identified a small intradermal bleb is raised over it, one-quarter of a cubic centimetre of anæsthetic solution being used in the two cubic centimetre syringe to which a small hypodermic needle has been attached. A two-inch 20 gauge needle is then introduced, first through the area of anæsthetized skin, and then through the sacro-coccygeal membrane, which is easily recognized at the time of puncture. With the patient in the position previously described, the line of direction of this needle at this stage is along a line running from the site of puncture to the patient's umbilicus.

Deep penetration of the needle at this point will identify the bony anterior wall of the sacral canal. However, in this anterior position are situated the venous plexuses, and puncture of these vessels results in an efflux of blood from the needle; consequently, once the needle has penetrated the sacro-coccygeal membrane, the line of direction is changed, and the needle is inserted for a short distance along the sacral canal parallel and deep to the sacral ridge.

The important information essential at this stage is to ensure that the needle has not penetrated the dura. To safeguard against this complication, the 20 cubic centimetre syringe is connected to the needle and gentle aspiration is carried out. The presence of cerebro-spinal fluid in the syringe indicates that the dura has been punctured, and such a finding warrants cessation of this procedure. However, should aspiration not produce any such return of clear fluid, the syringe is then removed from the needle, which is left *in situ*. The syringe is then filled with five cubic centimetres of air, and reconnected to the needle. This air is injected very slowly. If the needle has been inserted correctly into the sacral canal, the air will be injected easily, and no crepitus can be felt to palpation superficial to the line of the sacral ridge.

The syringe is again removed, but the needle remains strictly in its original position. Eight cubic centimetres of anæsthetic fluid are then drawn up into the syringe, which is connected again to the needle in the sacral canal, and this amount of solution is injected slowly. This is the test dose. Following this injection the patient is observed for five minutes, and at the end of that time she is asked to move her toes. Inability to move her toes indicates the production of spinal anæsthesia, and further injection is contraindicated. However, if muscle action of her toes is satisfactory, a further 20 to 25 cubic centimetres of the anæsthetic fluid is injected slowly. On completion of the injection, the needle is withdrawn and the site of puncture is swabbed with antiseptic. The patient is then placed on her back and her general condition is reassessed. She is then prepared for the necessary obstetrical procedure.

### Anæsthetic Agents Used in the Series.

"Xylocaine" and "Metycaine" were the local anæsthetic agents used. At the beginning of this series the "Xylocaine" 1% solution contained epinephrine, and with this solution some unsatisfactory complications arose which will be mentioned later. This complication arose in patients in whom blood was obtained from the needle following rupture of a vein of the anterior venous plexus. However, when a solution of "Xylocaine" 1% without added epinephrine was used, this complication did not arise.

"Metycaine" (1·5% solution) was used in a small number of cases, and a mixture of "Xylocaine" (1%) and "Metycaine" (1%) was also used. Dilution of the solution, when required, was always with normal saline. Sterile water produces a hypotonic solution, which is damaging to tissues. The average amount of solution used was 30 cubic centimetres, with a range extending from 20 to 40 cubic centimetres.

The reason for the small percentage of cases in which "Metycaine" (1·5% solution) was used is the fact that "Metycaine" in normal saline is very slow in its action; a period of at least ten minutes is required after the injection before analgesia is produced, and in some cases that period was twenty minutes. The other solutions were quicker in their action and therefore more popular.

"Metycaine" in Ringer's solution is stated to be rapid in action, but this combination was not used in this series. The use of the solution made from a mixture of equal parts of "Xylocaine" (1%) and "Metycaine" (1%) was also a time-consuming procedure, but very effective in its action.

### Results, Including Failures.

Table II indicates the frequency of the various procedures carried out in this series.

Table II includes only those cases in which the caudal analgesia was effective and was sufficient for the procedure involved. Twenty-one patients required additional anæsthesia, so that the failure rate was 7%. However, it was noted that the failure rate was in proportion to the technical experience of the member of the resident staff carrying out the injection.

### Causes of Failure and Other Complications.

As was previously mentioned, there were 21 cases of failure in the series. In six, generalized muscular twitch-

ings were observed, either during the injection of the solution or within two minutes of the completion of the injection. Three of these patients had evidence of severe preeclampsia prior to delivery, and all six cases occurred early in the series. At this time difficulty was experienced in obtaining supplies of "Xylocaine" without added adrenaline, and at the time of this complication the "Xylocaine" solution contained epinephrine, one to 200,000 parts. The complication did not arise when "Xylocaine" without epinephrine was used. Also all six cases with this complication occurred when introduction of the needle into the caudal canal produced a return of blood due to rupture of the venous plexuses on the anterior wall of the sacral canal. It was considered that the rapid absorption of the epinephrine by the intravenous route produced the convulsive movements observed, and in all six cases there was a pronounced and sudden increase in the blood pressure readings. All six patients received adequate oxygen therapy and three were given "Sodium Pentothal" by intravenous injection before delivery was effected. However, there were no other complications or sequelæ in these six cases.

Five patients were extremely nervous and required general anæsthesia to complete the forceps delivery. Five other patients were so obese that it was impossible to locate the sacral hiatus, and the procedure was then abandoned in favour of general anæsthesia.

In another patient, a *multipara*, the regional block was quite effective, but the presentation was by the brow and a general anæsthetic was administered to produce the deep anæsthesia required to carry out the necessary manipulations.

One patient had an idiosyncrasy to "Xylocaine". On completion of the caudal injection she became quite shocked, but she responded well to the hypodermic administration of "Neosynephrine". Delivery of the baby was quickly and easily carried out without any further anxiety. In another case the procedure was abandoned when there was a return of blood-stained fluid on introduction of the needle into the sacral canal.

Two patients suffered from retention of urine for forty-eight hours after delivery; one of these patients had suffered from nocturnal enuresis throughout her lifetime.

TABLE I.
*Anæsthetic Agents Employed.*

| Solution. | Number of Cases. |
|---|---|
| "Xylocaine" 1% .. .. .. | 273 |
| Mixture of "Xylocaine" 1% and "Metycaine" 1% .. .. .. | 20 |
| "Metycaine" 1·5% .. .. .. | 7 |
| Total .. .. .. .. | 300 |

Throughout the series there was no evidence of the production of spinal anæsthesia, nor was there any necessity to carry out intratracheal intubation. There was no evidence to suggest an increase in the rate of post-partum hæmorrhage, and there was no alteration to the prompt action of ergometrine by the intravenous route.

There was no maternal mortality or morbidity. There was one stillborn baby in the series, and this occurred in a *grande multipara*, who was delivered by forceps with the indication of delay in the second stage of labour. However, in this case the fœtal heart became inaudible when the os was dilated to admit three fingers. In this case also there was evidence of placental degeneration. There were no post-partum maternal complications of the respiratory tract.

It has been mentioned that throughout this series spinal anæsthesia was not produced owing to careful technique in the introduction of the needle into the caudal canal. However, should spinal anæsthesia be produced the results of such a misadventure depend on the level of ascending anæsthesia occurring in that particular case; the patient should be examined to determine the level of anæsthesia, and the details of her general condition, especially her blood pressure and pulse rate, should be recorded at regular intervals. The frequency of such readings would depend on the condition of the patient. Endotracheal intubation may be necessary, and in cases of respiratory failure mechanical respiration should be established and maintained until the patient recovers from the paralysis. "Methedrine" injected by the intravenous route (repeated if necessary) is recommended to combat the fall in the blood pressure.

TABLE II.

| Procedure. | Agent Used. | | |
|---|---|---|---|
| | "Xylocaine" (1%). | "Xylocaine" (1%) and "Metycaine" (1%). | "Metycaine" (1·5%). |
| 1. Repair of episiotomy .. | 57 | 1 | 1 |
| 2. Forceps delivery: | | | |
| (*a*) Head on perineum .. | 126 | 7 | 6 |
| (*b*) Low application .. | 40 | 5 | — |
| (*c*) Mid-pelvic application | 5 | 1 | — |
| (*d*) With manual rotation of fœtal head .. .. | 16 | 2 | — |
| (*e*) Face: left mento-transverse or left mento-anterior .. | 1 | — | — |
| 3. Manual removal of adherent placenta .. .. .. | 7 | 1 | — |
| 4. Delivery of twins .. .. | 2 | 1 | — |
| Total .. .. .. | 254 | 18 | 7 |

## Summary.

The accepted contraindications to caudal anæsthesia include precipitate labour, deformities of the maternal sacrum such as *spina bifida occulta*, great obesity of the patient, skin infections in the region, and *placenta prævia*. In this series of 300 consecutive cases there was a failure in 7% of patients to achieve satisfactory analgesia. In the analysis it was stated that five cases of failure occurred in obese patients; obesity is really a contraindication to the procedure, and the cause of failure may be incorrect selection of patients. However, the disturbing feature was the occurrence of convulsive seizures in six cases. In this regard there are two well recognized reasons for the production of "fits" with this procedure: (i) the presence of adrenaline in the solution used; (ii) the raising of the intracranial pressure by too rapid injection of the solution.

Mention has already been made of the satisfactory use of solutions without added adrenaline. Correct technique, in waiting for five minutes after the initial injection, is excellent prophylaxis against a rapid rise in intracranial pressure. The fact that in one case, after satisfactory caudal analgesia had been obtained, general anæsthesia was required to allow vaginal manipulation before the application of forceps, does show that, for the greater majority of labour ward procedures, caudal analgesia is very satisfactory.

However, it is stressed that both a thorough knowledge of the anatomy concerned and gentleness of technique are essential for satisfactory results. Also caudal analgesia may be used only when adequate means of resuscitation are available, and personnel experienced in modern anæsthesia, are available at the time of induction of the analgesia.

### Acknowledgements.

On behalf of the resident medical staff I desire to express our appreciation to Dr. Kevin McCaul, Director of Anæs-

thesia, Royal Women's Hospital, Melbourne, for his assistance and ever-available guidance. Without his help the compilation of this series of cases would not have been possible. Professor L. Townsend, members of the honorary medical staff, and Dr. J. C. Laver, Medical Superintendent, have given every encouragement and the facilities to carry out this series of investigations. My sincere thanks are also extended to my fellow members of the resident medical staff who assisted in carrying out this investigation. They were enthusiastic with this method of analgesia and went to endless trouble in giving complete details in the case histories.

# Reports of Cases.

## CAT-SCRATCH DISEASE IN WESTERN AUSTRALIA: A REPORT OF THREE CASES.

By JAMES R. H. WATSON,
*Perth.*

CAT-SCRATCH DISEASE was first described by Foshay in 1932. Since this time numerous reports have appeared in American and European literature. The disease follows a scratch by a cat. About a week after this occurrence, a papule may be noted at the site of the scratch; this is followed in a few days by enlarged, often tender regional lymph glands, which occasionally suppurate. The disease may be confirmed by a skin test with antigen made from pus from a previous case.

Stanley (1955) has shown recently that the serum contains complement-fixing antibodies to viruses of the psittacosis-*lymphogranuloma venereum* group.

The following would seem to be the first confirmed cases in Western Australia, although two patients have been presumed on good evidence to have had this disease previously (Price, 1955).

### Clinical Records.

CASE I.—A boy, aged seven years, had been playing with cats and kittens for a month. Ten days before he was examined, a gland in the left axilla underwent sudden enlargement and became painful. Two days later, a painful swelling increasing in size was noted on the inner aspect of the left arm. There was no fever or other constitutional disturbance. No scratch site could be remembered, but he knew he had been scratched at various times. He had no skin eruptions.

Examination of the patient revealed an enlarged gland in the left axilla, the size of a small walnut, freely mobile and painful to touch. In the middle of the medial aspect of the arm a tender, freely mobile mass of the same size was palpable. The epitrochlear glands were not enlarged. General examination revealed no abnormality. The Mantoux test failed to produce a reaction. An examination of the blood gave the following information: the hæmoglobin value was 13·8 grammes *per centum*, the erythrocytes numbered 4,380,000 per cubic millimetre, and the leucocytes numbered 8200 per cubic millimetre, 64% being neutrophile cells, 35% lymphocytes and 1% eosinophile cells.

The patient was observed for a week, and no fever, constitutional disturbance or change in the size of the glands was noted. Eighteen days from the time when glandular enlargement had been first noted, a necrotic gland was removed from the inner surface of the arm. Dr. V. Fergusson-Stewart reported that the microscopic picture of this was consistent with a diagnosis of cat-scratch disease, examination of sections showing prominent follicles with œdema and monocytic infiltration, especially in the peripheral areas. A skin test three days after operation with 0·1 cubic centimetre of antigen given intradermally produced a strongly positive reaction within forty-eight hours. Serum contained complement-fixing antibodies to psittacosis virus to a titre of one in 20. The axillary glands subsided five weeks after the onset.

CASE II.—A female child, aged two and a half years, was examined three weeks after the occurrence of a small papule on the dorsum of the right wrist with associated axillary adenitis. There was no history of a cat scratch, but the family had owned a cat which was destroyed one week after the symptoms began because it was ill. The illness was not accompanied by fever or constitutional disturbance. The intradermal injection of cat-scratch antigen gave a positive result. The patient's serum contained complement-fixing antibodies to the psittacosis virus to a titre of one in 20.

CASE III.—A boy, aged two and a half years, when first examined by Dr. C. W. R. Price in July, 1954, had a four days' history of right axillary adenitis, preceded by a scratch on the right hand a few days before. Examination of the patient revealed a fluctuant mass fixed to the skin, which was discoloured. Greenish-yellow pus was aspirated from the abscess; attempted culture of microorganisms from this was unsuccessful. The glands in the site were excised. Examination of sections of a gland revealed a necrotic mass surrounded by aggregations of lymphocytes, epithelioid cells and giant cells. The Mantoux test failed to produce a reaction. There was mild fever before and after operation, but no constitutional disturbance.

In June, 1955, intradermal injection of a cat-scratch antigen gave a positive result. The serum contained complement-fixing antibodies to psittacosis virus to a titre of one in 40.

### Discussion.

These patients had a good story of contact with cats, but the lack of a local lesion made diagnosis difficult in Case I. Daniels and MacMurray (1954), who analysed 160 cases of cat-scratch disease in the United States of America, state that in only about half of their cases did a primary skin lesion develop. These authors also state that low fever and mild systemic symptoms are frequent. They find the disease to involve commonly the axillary, cervical or inguinal nodes. Waters *et alii* (1952) stress the point that fever may be variable or absent.

The disease is usually mild, but severe cases with encephalitis have been noted. Rashes, including *erythema nodosum*, do occur but are infrequent.

Recession of glands to normal takes three weeks to two months (Large, 1951). The lack of lymphangitis is noteworthy.

No ætiological agent has been isolated. All cats so far incriminated have been healthy (Smith, 1952).

It is probable that patients with cat-scratch disease have been thought to have tuberculous gland enlargement in the past. The superficial histological resemblance of these two entities is pronounced, and has probably encouraged this mistake.

Conversation with veterinary surgeons dealing with small animals has stirred memories of odd illnesses of similar nature in themselves and their employees in the past. A survey of this group might well reveal a new occupational disease.

### Summary.

1. The presence of cat-scratch disease in Western Australia is reported for the first time.

2. The clinical features of the disease are discussed briefly.

3. The disease may be an occupational hazard of veterinary surgeons and their assistants.

### Acknowledgements.

The antigen was made available through the kindness of Dr. N. F. Stanley, Institute of Epidemiology and Preventive Medicine, Prince Henry Hospital, Sydney, who arranged the complement fixation tests also. I am indebted to Dr. C. W. R. Price, who made available his notes on Case III, and arranged for me to examine the patient in Case II.

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## PERFORATED TYPHOID ULCERS AND PERITONITIS.

By S. A. MELLICK, F.R.C.S.,
*Brisbane.*

TYPHOID FEVER is very rare in Brisbane today. As recently as three decades ago whole wards in public hospitals were filled with patients who were suffering from typhoid infection; and in such patients perforation of the bowel was a clinically detectable surgical condition. Before the present case, the last known perforation of a typhoid-infected intestine occurred at the Brisbane Hospital in 1944, and the perforation was not diagnosed until the autopsy was performed. It is considered of interest to record the present history, especially in view of the satisfactory response by so ill a patient to specific therapy, and more especially as a reminder that the possibility of a typhoid infection should not be forgotten in surgical wards.

### Clinical Record.

A male patient, aged forty-five years, was admitted to the Brisbane Hospital at 6 a.m. on March 3, 1952. He had been perfectly well until twelve days previously, when he developed fever, vomited once and then had diarrhœa (four or five motions per day, fluid consistency, with no blood, pus or mucus). There was slight generalized mid-abdominal pain with the diarrhœa. He rested in bed and improved a little over the intervening twelve days until three hours prior to his admission to hospital, when he developed, whilst in bed, sudden, severe, constant, lower abdominal pain which forced him to lie very still and made him nauseated. There was no shoulder pain.

On examination the patient was found to be a pale, thin man in severe pain, with rapid, thoracic-type breathing. The skin was blotchy and cold. The blood pressure was 120 millimetres of mercury, systolic, and 90 millimetres, diastolic. The pulse rate was 120 per minute and the pulse was of very poor volume. The temperature was between 101° and 102° F. The tongue was dry and furred. The abdomen was found to be distended below the umbilicus and there was some moderate generalized tenderness with rebound tenderness maximal in the right iliac fossa. No peristalsis was heard on auscultation. Liver dullness was present and of normal extent. On examination *per rectum* there was slight tenderness high up anteriorly. The provisional diagnosis was one of general peritonitis due to a ruptured appendiceal abscess.

Treatment was commenced with penicillin and streptomycin by the intramuscular route and serum transfusion was begun into a vein. By twelve noon the patient's general condition was better, his pulse was stronger, and he appeared to be a better colour.

A laparotomy was performed under general anæsthesia. Much thick, creamy, non-odorous pus was discovered in the pelvis and the right lower quadrant of the abdomen, with thin pus elsewhere in the abdomen. The terminal few feet of ileum were much inflamed, with many small indurated areas where the bowel was almost perforated. There were found to be three open perforations of the ileum, each one about a foot from the ileo-caecal valve, and all close together. The largest was a quarter of an inch in diameter. The caecum and appendix were found to be normal. A biopsy specimen was taken from the edge of the largest perforation, the holes were oversewn with chromicized catgut and the abdomen was closed. The diagnosis was now considered to be one of typhoid fever, and a sample of blood was removed for culture, for the performance of a white cell count, and for a Widal test. As soon as the patient became conscious chloramphenicol administration was commenced by mouth in a dosage of three grammes initially and two grammes twice a day.

The blood culture produced *Salmonella typhi*, phage type "N". Biopsy of the ulcer revealed a process of acute inflammation and necrosis with a monocytic exudate in the floor of the ulcer. The Widal test gave a positive result for *S. typhi* "H" suspension in a dilution of one in 640. The leucocyte count remained between the figures of 6000 and 8000, with a normal differential count, throughout the patient's stay in hospital. Chloramphenicol administration ceased on April 10, 1952. Thereafter four alternate-day stool cultures gave negative results for pathogenic organisms. The patient was discharged from hospital on May 1, 1952. He has remained well since then, and in August, 1955, no *S. typhi* organisms were found in his stools. The original source of infection of this patient was never traced.

### Discussion.

There is still considerable divergence of opinion whether or not operation is helpful to patients with advanced generalized peritonitis. In this instance it was thought that drainage might help to maintain the initial favourable response to resuscitation, and so laparotomy was performed. In fact it was the means of making the diagnosis in this case and of instituting specific treatment, without which survival probably would not have ensued.

In pre-antibiotic days, perforation of the intestine complicated typhoid fever in about 1% to 5% of cases, and was the most common surgical complication of the disease. In 95% of perforations the ileum is the offending site, and all the perforations occur in the terminal three feet. Rarely the perforation is situated in the large bowel, the appendix, Meckel's diverticulum or the jejunum. The perforation is single in 84% of cases (Moynihan, 1905). The mortality rate of perforated typhoid ulcer, when operated upon, varied between 70% and 90%, and death was almost inevitable without operation (*Lancet*, 1948).

Lozoya (1948) reported a series of 21 cases of perforated typhoid ulcers occurring in children, treated by operation and penicillin therapy. The mortality rate in these cases was 57%. Woodward (1948) and Stevenson and Welbourn (1949) reported such cases of perforation treated successfully without operation, but with chemotherapy, the first-named using chloramphenicol, penicillin and streptomycin, and the latter two using penicillin and sulphasuccidine. El Ramli (1950), in treating 200 patients suffering from typhoid fever with chloramphenicol, had seven cases of perforation during the treatment, and Woodward (1948) also agreed that, although chloramphenicol had reduced the mortality rate of typhoid fever to something less than 1%, it was possible for a typhoid infected intestine to perforate whilst under treatment.

All medical authorities appear to have used a combination of drugs in the treatment of typhoid perforations. However, in the past few years it has been shown that the concomitant use of penicillin and chloramphenicol may be harmful, since the two drugs are antagonists (Jawetz, 1952). It would seem that chloramphenicol alone should be used in the treatment of these patients, especially now that it is available for parenteral administration.


### Acknowledgements.

I should like to thank Professor Neville Sutton, Senior Surgeon, Brisbane Hospital, under whose care this patient was admitted to hospital, for his guidance and help in the management of the patient; Sister M. Lochrin and her staff for their diligent nursing attention; and also Dr. A. D. D. Pye, General Medical Superintendent, Brisbane Hospital, for helpful suggestions and for permission to publish this case.

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# Reviews.

**Obstetrical Practice**, by Alfred C. Beck, M.D., and Alexander H. Rosenthal, M.D.; Sixth Edition, 1955. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 10" × 7", pp. 1080, with many illustrations. Price: £6 12s.

THIS book by Beck and Rosenthal is a large volume containing all the essentials of this subject, more particularly as practised in New York. This sixth edition brings the book right up to date. The paper is of excellent quality, and apart from its size, the book is eminently readable. The illustrations are outstandingly good throughout and better than those in most other text-books.

It is difficult to pick out any part of such a book for comment but the chapters on Cæsarean section, analgesia and anæsthesia are outstanding.

Estimations of pelvic capacity are explained in clear and easy detail. Every now and again short historical flash-backs create an interesting background for the young obstetrical reader.

Mechanisms in all presentations are set out in detail and cannot help but make for an intelligent understanding of this essential basis of midwifery.

The subject of preeclamptic toxæmia is reasonably well covered, but excessive weight gain cannot be efficiently detected by only monthly weight checks, and systolic blood pressure readings are emphasized to the detriment of the far more important diastolic pressures; nor is enough importance given to the question of relative increase. An inexperienced reader of this text-book would gather erroneously that eclampsia must still continue to appear suddenly in quite a percentage of his patients.

In dealing with breech presentations, the standard Mauriceau-Smellie-Veit manœuvre is illustrated and described rather sketchily, and it is a pity that other methods are completely ignored. More especially, in this country, the Lovesett technique has come to be regarded as the greatest advance in breech management. However, with such exceptions, the book can be recommended as thoroughly sound in its teachings, and as an excellent reference book to have in the library.

**The Year Book of Radiology (1955–1956 Year Book Series)**, edited by John Floyd Holt, M.D., and Fred Jenner Hodges, M.D.; 1955, Chicago: The Year Book Publishers, Incorporated. 9" × 6", pp. 413. with many illustrations. Price: $9.00.

THE editors of the "Year Book of Radiology" (1955–1956 Series) have had a colossal task in preparing a review of the advances in radiology appearing in the radiological journals of the world. Advances are reported in all branches of the specialty, especially in the various forms of angiography. Image amplification is being gradually improved and its cost lessened. Improvements are also seen in photographic methods and in apparatus. Tomography is becoming more popular with new technical methods. This is noted specially in the study of the larynx. A new roll film device allows of rapid exposures (five to the second) which are of value in angiography of the chest and renal tracts. Xeroradiography is a new method of producing radiographs by exposing a part on a selenium plate and dusting with a fine powder when an X-ray picture is produced in two minutes. This picture may then be wiped off and the plate is ready for another exposure. In chest work a pair of films is exposed (one with a specially fast pair of intensifying screens) and one film will show the lung structure and the other mediastinal detail. An ingenious method has been devised for producing an X-ray image and a photograph of the skin surface at the one time and then superimposing the negatives and printing a composite photographic print. Mucosal patterns are still being studied and a water-soluble lead salt, which is non-poisonous, is being used with good results. Many interesting pathological conditions of various regions are described and illustrated. A magnet has been found of use in removing metallic foreign bodies from the stomach. Several interesting lesions of the pancreas are described, together with advances in technique in studying this organ. Radiation therapy has been improved by the use of radioactive isotopes, by the use of the cobalt beam and by rotational therapy. Techniques generally are being simplified and in the study of the various organs undergoing treatment details of application of dosage are carefully detailed. The whole work is full of interesting reports and the illustrations are of the highest quality. The work is well worth close study.

**Life Stress and Essential Hypertension: A Study of Circulatory Adjustments in Man**, by Stewart Wolf, M.D., Philippe V. Cardon, jnr., M.D., Edward M. Shepard, M.D., and Harold G. Wolff, M.D.; 1955. Baltimore: The Williams and Wilkins Company. Sydney: Angus and Robertson, Limited. 9" × 6", pp. 262, with illustrations. Price: £4 2s. 6d.

THE authors have endeavoured to discover whether "the stresses of modern civilization" have any ætiological significance in essential hypertension by surveying work done at Cornell Hospital during the last decade.

This was an investigation into the circulatory adjustments associated with "stress interviews" with patients with essential hypertension and normal controls. Data include pulse rate, cardiac output, peripheral resistance and renal flow. The stress interview frequently elevated the blood pressure.

When the patient was overtly angry peripheral resistance was lowered, but outward calm and inward seething raised it.

A detailed survey of 26 patients illustrates not only the elevation of blood pressure produced by stress but also the fall during relaxation. Exploiting the latter led to the return to normal pressure levels for a number of years in some cases, even where sympathectomy had been unsuccessful. A review of the treatment of essential hypertension notes the effects of modern measures which are of most value in tiding over an acute phase with encephalopathy, cerebral vascular accident or pulmonary œdema.

The authors contend that hypertensives frequently feel compelled to try to excel but at the same time to avoid open conflict, thus creating dilemmas. Psychotherapy must therefore show the patient that he feels threatened, and therefore anxious, but that he must meet this with direct action. In many of their patients this process led to a fall in pressure. They therefore recommend a serious interest in the life experience *et cetera* of the patient in the hope of helping him to a more constructive adjustment.

This book stimulates thought on one section of a complex problem and provides a rational explanation of the action of emotional factors in hypertension.

# Books Received.

*[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]*

"Current Therapy, 1956: Latest Approved Methods of Treatment for the Practising Physician", edited by Howard F. Conn, M.D.; Philadelphia and London: W. B. Saunders Company. Melbourne: W. Ramsay (Surgical), Limited. 8" × 10½", pp. 662. Price: £5 10s.

This is the eighth edition of an annual series and is intended for the practising physician.

"Methods of Biochemical Analysis", edited by David Glick; 1956. New York: Interscience Publishers, Incorporated. London: Interscience Publishers, Limited. Volume III. 9" × 6", pp. 447. Price: $9.50.

This is an annual production.

The Medical Journal of Australia

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*All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words of phrases.*

*References to articles and books should be carefully checked. In a reference the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those adopted by the Quarterly Cumulative Index Medicus. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.*

*Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.*

## THE NUTRITIONAL WORK OF FAO, WHO AND UNICEF.

VERY soon after the United Nations was inaugurated and its Charter adopted in 1946, specialized agencies were set up to help to care for the health and nutrition of millions of under-privileged people in war-torn Europe and in Asia and Africa and later South America, Central America and Oceania. The first of these agencies was the Food and Agriculture Organization (FAO) set up in 1946. The World Health Organization (WHO) was formally established in 1948. The head office for this is in Geneva, but there are regional committees and offices for Africa, the Americas, the Eastern Mediterranean, Europe, South-East Asia and the Western Pacific. The United Nations Infants and Children's Emergency Fund (UNICEF) was created in 1946 to help the children of war-devastated countries. It was reconstituted in 1952 to help children particularly in under-developed countries. In 1948 the Executive Boards of UNICEF and WHO established a joint policy committee to direct their joint programmes. At a special symposium held by the Nutrition Society at Oxford in July, 1955,[1] the director of FAO, W. R. Aykroyd, presented an account of the aims and services of FAO, the director of WHO, R. C. Burgess, did so for the nutritional activities of WHO, and the Secretariat of UNICEF gave an account of the assistance given by UNICEF in child nutrition in various countries. In addition there were papers on nutrition and home economics programmes in Egyptian villages and nutrition work in Burma. The broad aims of FAO cover a wide field related to agriculture, food preparation and distribution, fisheries, forestry and economics. One of the expressed aims is "to raise levels of nutrition". In the early stages the nutrition division was helped by the Standing Advisory Committee on Nutrition, a body made up of prominent world figures in the field of human nutrition. This was replaced in 1951 by a joint FAO-WHO Expert Committee on Nutrition, which has held several meetings. It consists of well-known nutritionists invited by the Organization, and it advises the Directors-General of FAO and WHO on the problems of nutrition which might receive the attention of the two organizations and helps in coordinating their activities. It also advises either or both Directors-General of any technical problems on nutrition presented to it.

The general aim of the division is to see "that people get enough of the right sort of food to eat". In attempting to improve nutrition, one must know something about existing consumption levels, so one of the activities of FAO is the establishment of "Food Balance Sheets" in each country where help is to be given. These of necessity at the present time have a high margin of inaccuracy, but they are necessary and helpful even when incomplete. Where possible FAO works with local organizations in obtaining the necessary information. The efforts to persuade governments to make dietary surveys have not been very successful. Aykroyd points out that the various social and psychological, as well as the economic and agricultural, factors must be studied; for if education in nutrition is to be effective, the various reasons why people eat what they do in the way they do must be taken into account. Requirements for calories and protein and other nutrients have been studied for many years, and tables of "recommended allowances" have been published. These are still not very satisfactory in practice, and FAO has set up committees to study and report on various aspects such as calorie requirements. The study of proteins has come to have special significance, and a conference sponsored jointly by FAO, WHO and the Josiah Macy, Jr. Foundation met in June, 1955, to study protein requirements in practice. Young children, during and after the period of weaning, suffer most severely from protein malnutrition. Among the problems studied by FAO are the relative effectiveness of animal and vegetable proteins or mixtures of vegetable proteins. Put simply the question is: "Is milk a necessary food for children?" This question is of enormous importance in many countries where dairy farming is difficult or milk cannot be transported and kept uncontaminated satisfactorily. The enormous quantities of dried skim milk stored in various countries are helping at present, but these will run out in time. Training nutrition workers and teaching people in their own homes represent another aspect of the activities of FAO. Foods can be recommended, but unless there is a demand and liking for them, they will not be eaten, and education and persuasion of the consumer are very important. A great deal is being done in training selected people from the countries being helped in nutrition generally by means of Fellowships at some suitable centre in Europe or America. Medical men and others from various territories in Africa have been given short nutrition courses. FAO is naturally interested in rice, the main food of half the world's popu-

[1] *Proc. Nutrition Soc.*, 1956, 15 : 1.

lation, and has given much attention to improving the rice-eater's diet, as, for example, by rice enrichment.

The nutrition section of WHO is a small unit. WHO is concerned with all aspects of health, and malnutrition is probably one of the most important causes of illness in the world today. One of the big investigations carried out by WHO in this field is concerned with epidemic goitre. Where refined salt is in general use, the addition of potassium iodide or iodate to the salt has been found satisfactory; but where crude salt is used, there has been no adequate method of iodizing it. This is being investigated, as also are other methods of giving iodine. The disease known as kwashiorkor has been studied intensively by FAO staff members and committees set up by WHO, and surveys have been carried out in Africa, Central America and Brazil. Vegetable protein substitutes for milk have been studied on a large scale. The pioneer work done in Germany by a British Medical Research Council team is being continued by WHO in several countries, particularly Africa, India, Indonesia and Central America. An important function undertaken by WHO is education in the use of locally available foods. Here there are great difficulties to be overcome because of the maze of tradition, taboo and magic and of the whole system of belief of peoples in the use of certain foods. After some early mistakes WHO has turned to the social anthropologist in an attempt to determine in what way prevailing beliefs and practices influence the acceptance of active measures, and several anthropologists are making studies in different parts of the world. Other important activities of WHO concern the control of pellagra and the study of atherosclerosis and nutritional anæmias.

The exclusive function of UNICEF is to aid government programmes that result in benefits for children, and aid is primarily in the form of imported supplies and equipment, as contrasted with the technical assistance given by FAO and WHO. After a preliminary period of continuing the work of the United Nations Relief and Rehabilitation Agency in aiding war-devastated countries, mainly in Europe, the aid was, in 1947, extended to all countries where it was necessary. The major nutritional principle adopted was to limit UNICEF aid to the provision of supplementary foods of high nutritive value, especially foods rich in proteins, emphasis being placed on the provision of dried milk. The participating governments were expected to provide other foods required (usually cereals, potatoes and vegetables) out of local funds. The peak year of assistance was reached in 1950 with about six million beneficiaries in twelve countries. By the end of 1955 UNICEF will have shipped or allocated for shipping about 700,000,000 pounds of dried skim milk. In addition it has allocated the equivalent of over £3,500,000 for milk conservation projects. UNICEF aids countries in establishing permanent facilities for collecting, conserving and distributing safe milk from local supplies and aims to do it in such a way that the countries will be able to provide free or low-cost milk to large numbers of children. UNICEF provides the equipment for drying and pasteurizing plants, the governments providing the buildings, labour *et cetera*. By 1951 UNICEF shifted the main emphasis of its work from Europe to under-developed countries in Asia, Central and South America and recently Africa. UNICEF has given aid for sixteen drying plants in under-developed countries and thirteen fluid milk plants. There is a preference for milk drying rather than fluid milk plants for a variety of reasons. The demonstrations of the use of dried milk have been greatly helped by the enormous stores of skim milk powder held by the United States and supplied free by them. As supplies will probably last till 1958, continuing programmes of aid may be a stimulus for more permanent solutions in many countries. UNICEF also helps in school feeding programmes, but only where there is a need and where sufficient local resources are available to run them satisfactorily. As surplus skim milk powder supplies will run out, UNICEF has interested itself in the development of locally feasible methods of producing fish flour and vegetable proteins in a form suitable for young children. The Home Economics Section of WHO promises to be very useful in the education of women in the best use of available foods, and a good start has been made in Egyptian villages where a trained home economist, with the assistance of the Egyptian Government, is doing fine work.

The international organizations, FAO, WHO and UNICEF, like other organizations of the United Nations, do not give direct service to the people of the world. Each government is responsible for the welfare of its people; international organizations, when the governments ask them, help governments to carry out that responsibility. The nutrition programmes described are therefore mainly programmes of governments. They illustrate how international assistance works out in practice, and their great success in adding to the welfare and happiness of the world makes one hopeful that similar cooperation in other matters will help to make the world a happier place to live in.

# Current Comment.

## MORE ABOUT MEDICAL WRITING.

IN a delightful note recently ("The De-ists") Sir William MacArthur dealt adequately with his reasons for rejecting, editorially, neologisms of the "delouse" and "deflea" kind.[1] He pointed out that "to louse" and "to flea" have been used in classical English for centuries, and that *pediculare*, not "de-pediculare", is the Latin word, and he suggested that ignorance of good English usage was responsible for the introduction of the unnecessary hybrids during the first World War. He mentioned *en passant* those etymological monsters, "hospitalization" and "deratization"—surely, however, they are products, not of ignorance, but of exhibitionism or of capacity for copying.

In October, 1955, the *International Record of Medicine* published a symposium on medical writing. H. E. Sigerist mentions that he is not quite sure that there is such a thing as "medical writing"—there are good writing and bad writing; style must naturally vary according to the subject, and a written paper requires more formality of expression than does an address, for instance. Sigerist's two prerequisites for good writing, particularly on scientific subjects, are clear thinking and command of the language. He points out that the English language is a marvellous instrument of precision and clarity. Here we have the first link with MacArthur's argument—lack of command of the language is responsible for inability to choose the precise word which would convey the exact

[1] *Tr. Roy. Soc. Trop. Med. & Hyg.*, May, 1955.

shade of meaning required, for English is outstanding as a language of many apparent synonyms—quite large groups of words with approximately the same meaning, but each with its own particular shade of that meaning. Lack of command of the language, too, is responsible for the construction of poor sentences—those, for instance, which leave their meaning in doubt, or those which need to be read two or more times before their meaning becomes clear. The first criterion of good writing is that each sentence, read only once, shall convey its full meaning immediately. In this connexion, however, Sigerist deplores the general recommendation that scientific papers should be as short and as factual as possible—as a result, he states, "they are informative, to be sure, but they make frightfully dull reading". This, of course, is not necessarily true. His other prerequisite, clear thinking, will ensure that the paper expresses its argument clearly and fully, and carries it smoothly from its defined beginning to its logical end, so that it should not be dull. A recent writer in the editorial columns of *The Advertiser* (Adelaide) described several requisites to clear thinking—accurate knowledge, ability to see things in their right perspective, intellectual honesty and a right understanding of words. Among the hindrances to clear thinking were prejudice and prepossession and reluctance to acknowledge the fact that we live in a swiftly changing world.

To qualify Sigerist's "should not be dull", we must turn to Hans Selye, who, in his contribution to the symposium, entitled "How Not to Write a Medical Paper", states that the essential part of medical writing is the evaluation of the pros and cons, first for making observations, then for describing them, and finally for drawing conclusions from them. That is to say, if the subject is not worth discussing, do not write about it. Much magnificent writing on trivial themes exists in the literature, but there it is the style that impresses the reader; no amount of style will make a mediocre scientific subject anything but dull. Yet, like Sigerist, Selye suggests that to present data in an austere, factual and concise style, shorn of all unessentials, is to court criticism for being unimaginative and for presenting a dull catalogue of facts; that to make even the most technical report vivid by showing the broader implications of the work in polished and eloquent prose, is to risk the accusation of showmanship. This last little extravagance of Selye's, however, defeats his purpose. True, an Osler can be read with delight in his polished and eloquent prose—but few people, and a far smaller proportion of medical men, are capable of producing clear and lucid prose, much less of polishing it.

Another requirement for avoiding dullness is that the author must really know his subject intimately, and must have expended a lot of time and work on it. The next paper in the symposium is by Hugh Clegg, editor of the *British Medical Journal*. He commences by deploring the tendency of contributors, eager for priority, to rush in with papers based upon too few observations, made without adequate control—and the tendency of editors to accept them. Then he discusses the habit of dragging in innumerable references to give the illusion of weight and learning to an otherwise slight paper, and of including impressive tables and charts which are valueless unless the data on which they are based are also included—in which case they become unnecessary. Clegg's next observation is an important one. Sigerist implied that obscurity in expression was due to poor command of the language, but Clegg points out that it is most commonly due to poor familiarity with the subject. Next, he condemns the use of medical jargon, and of superfluous words and roundabout phrases, which are commonly used to pad out scant material. Above all, he condemns the use of words without knowledge of their precise meaning, and advises free consultation of the "Concise Oxford Dictionary": "If people knew the meanings of the words they speak and write life would be simpler and more harmonious." Finally he has a word of comfort for those doctors who find composition difficult: "Few if any are likely to write a scientific article as if it were to be a contribution to belles lettres." This is sound and practical, in contrast to the idealism of Sigerist and Selye. To achieve the best results, Clegg advises use of the active instead of the passive voice, and concrete rather than abstract nouns; he recommends avoidance of long and complicated sentences, and he counsels aiming at simplicity, lucidity, clarity and brevity. Another editor, Walter C. Alvarez, of *Modern Medicine*, points out that the wastepaper baskets of editors and of readers are stuffed with the writings of doctors who did not stick to the point and did not make things simple.

To end the symposium there is a fine essay, "Books in the Physician's Life", by Félix Martí-Ibáñez. Earlier, Sigerist advocated wide reading of good literature as an aid to writing. Martí-Ibáñez deals with text-books and current journals, recreational reading, and humanistic reading, and he even offers advice on finding time to read. If his advice is taken, then perhaps Sigerist's plea for better writing through better reading may be realized—but simple, lucid, concise writing about a worth-while subject with which the author is completely familiar will always produce the best papers.

## THERAPY OF THE MALIGNANT LYMPHOMATA.

THE malignant lymphomata comprise a group of uncontrolled neoplastic conditions of the lymphoid system. They resemble both the sarcomata and the leuchæmias, though characteristically the neoplastic growth of the lymphoma and its secondary deposits tend to remain confined to the lymphoid system. Death is the usual outcome, though the prognosis of the disease may be for a very slow progress. As for the other malignant neoplasias, little is understood about the nature of the condition, and, like most of the sarcomata, treatment is infrequently successful in cure despite considerable alleviation of the signs and symptoms for varying periods. The group of malignant lymphomata includes the relatively slowly progressive Hodgkin's disease and the follicle lymphoma, and the rapidly malignant lymphosarcoma and reticulum cell sarcoma. A study of 116 patients with these diseases has been made by C. A. Hall and K. B. Olson[1] with the particular objective of evaluating the effectiveness of nitrogen mustard both as a sole and as an additional therapy in association with long-term follow-up studies. The patients were all those admitted with malignant lymphoma to the Albany Hospital, New York, in the eleven years up to the end of 1950. Each case was proved on histological grounds and no patient had been previously treated. Patients were treated by radiotherapy of selective local type and by nitrogen mustard. Some patients received both treatments and others were treated by surgical means only. Nitrogen mustard was used only when the disease was no longer localized. Of three patients with Hodgkin's disease treated by excision of affected glands, two survived for very long periods, but it was considered that this apparent success was due to the relatively benign nature of the condition. Forty-eight patients with Hodgkin's disease were treated initially by radiotherapy. The response to this treatment was widely variable; 34 obtained a remission of some kind and nine patients survived for five years. The response to particular dosages and to repeated treatments varied so greatly that no patient received exactly the same treatment. In many patients outlying and untreated diseased areas either failed to progress or regressed when the therapy was applied to the major affected areas. Subsequent response to nitrogen mustard in these patients was brief. The response of 24 patients treated initially by radiotherapy varied widely; 20 of them obtained a remission. Despite the addition of nitrogen mustard in some cases, there were no survivors. Of 13 patients with generalized Hodgkin's disease who received nitrogen mustard initially, 11 obtained a remission of varying extent up to six years. Usually individual remissions were short and became increasingly brief with succeeding treatments. The five-year survival time was rather less for the group treated by nitrogen mustard than for the radiologically treated group, though, as the authors point out,

[1] *Am. J. M.*, March, 1956.

nitrogen mustard was used only as the initial treatment when Hodgkin's disease was already widely disseminated. No proof was available to show that nitrogen mustard was effective after the development of radio-resistance. Of nine patients with lymphosarcoma, only two failed to respond to initial therapy with nitrogen mustard and the longest total remission lasted for eighty months. Again no remission occurred with nitrogen mustard in radio-resistant cases of the disease. From these results it appears that nitrogen mustard and radiotherapy are in general equally, though for individuals variably, effective in the treatment of the malignant lymphomata. A comparison of data before and after the introduction of nitrogen mustard does not indicate any great improvement in the outlook for patients with one of the malignant lymphomata.

In a further review in the same journal, Hall and Olsen have collected and reported on the therapy of the malignant lymphomata from the published papers of other investigators. The figures vary considerably, but do not indicate any superiority of either surgical or radiological methods in the treatment of any of the malignant lymphomata. While there is considerable evidence that localized lymphosarcoma is sometimes curable, the best that can be hoped for with Hodgkin's disease is a long remission. Because of considerable differences in the manner of compiling statistics, only rough comparisons are possible between different series. It is impossible to be certain that the use of higher voltage fractional dosages of X radiations has increased the survival time, though there may be some improvement with total body irradiation. It is not certain that the use of high local doses of radiation with small amounts of radiation to the neighbouring areas is more effective than conventional therapy. Results of the use of X radiotherapy in the treatment of lymphosarcoma suggest a reduction in the morbidity with the application of modern techniques, though there may be little effect on the survival time. The variably benign nature of Hodgkin's disease makes evaluation of nitrogen mustard difficult, though on the whole other authors tend to regard it as less efficient than radiotherapy. However, nitrogen mustard may be preferable in the presence of mediastinal obstruction. Only in the later stages of the disease is the blood marrow less resistant to nitrogen mustard than is the neoplasm, so that nitrogen mustard is a danger to the hæmatopoietic system only when it is no longer effective in Hodgkin's disease. In cases of lymphosarcoma, nitrogen mustard may be effective, but its use is not the method of choice when the disease is localized. The use of triethylene melamine in the lymphomata has not been attended by any improvement over nitrogen mustard therapy, and the former drug is less predictable. The use of ACTH and cortisone has resulted in some brief remissions, though the chief effect of these drugs is the increase of hæmatopoiesis in patients with a hypocellular bone marrow. Hall and Olsen conclude that surgery and radiotherapy are equally effective in the treatment of localized lymphosarcoma. Apart from these occasional cures, there is no further evidence that treatment usefully prolongs the survival time, though there is no doubt that symptomatic improvement does occur.

## A REPORT ON DIVINE HEALING.

THE British Medical Association in London has issued a pamphlet[1] entitled "Divine Healing and Co-operation Between Doctor and Clergy". It contains a memorandum of the evidence submitted by a special committee of the Council of the Association to the Archbishops' Commission on Divine Healing, together with three appendices. In January, 1954, the Association received a request for assistance from the Archbishops' Commission on Divine Healing and Co-operation Between Doctors and Clergy. The Association's views were particularly sought on the following points:

> (1) What evidence can the medical profession submit of (*a*) spontaneous cures of apparently incurable disorders; (*b*) rapid or accelerated recovery from serious illnesses which appear to have resulted from anything which might be called "spiritual ministrations"?
>
> (2) Is there any available evidence of the value—physical and psychological—of healing services, the laying on of hands, unction, and the influence of public or private prayer?
>
> (3) In what circumstances are the above practices of value or attended by possible harmful effects, including the risk of delay in seeking medical advice?
>
> (4) Evidence of co-operation between doctors and the clergy and methods through which this has been achieved.
>
> (5) How can this be encouraged and extended in general by co-operation centrally between medical and Church organizations, and locally between doctors and parish priests, with particular reference to hospital and general practice?
>
> (6) What measures could be promoted so that the clergy can give assistance to the medical profession in dealing with the spiritual needs of their patients, their attitude to their illnesses, assistance over convalescence, rehabilitation or resettlement?

The request was referred to an *ad hoc* committee consisting of the Association's six representatives on the Churches' Council of Healing. The committee was given powers of cooption and coopted four additional members. An invitation to join was extended to three Roman Catholic doctors who are prominent members of the medical profession, but they were unable to accept the invitation. The membership of the committee was as follows: Dr. Mary Esslemont (chairman), Dr. E. E. Claxton, Dr. Peter Edwards, Dr. Robert Forbes, Dr. Doris Odlum, Dr. H. D. H. Sutherland. The coopted members were: Dr. G. J. Alexander, Dr. E. A. Bennett, Dr. Cuthbert E. Dukes, Dr. J. A. Hadfield. The committee got others to assist in its discussions and in the framing of its report.

The committee finds it difficult to define health and healing. Health is a "condition of satisfactory function of the whole organism". The words health, wholeness and holiness are closely linked in origin. Healing, we are told, may be described as "the process by which a living organism, whose functions are disordered, is restored to health or 'made whole', that is to say, returns to complete functioning". Perfect health is rarely attained, and with most cases there is a residue. The patient's criterion of healing is freedom from symptoms; the doctor's standard is the restoration as far as possible of normal anatomical structure and physiological function. The types of illness said to be cured by spiritual healing fall into two categories: (*a*) psychogenic and psychosomatic disorders, and (*b*) organic conditions. Under the heading of psychogenic and psychosomatic disorders the following two paragraphs appear:

> Relief of psychogenic disorders appears to depend partly on the individuality of the patient and on his capacity to respond, partly on the personality of the healer with his power of suggestion, and to some extent on the method employed. The same drug given by two doctors may have a very different effect according to the personality of the practitioner administering it. Thus one may succeed where another fails; one patient may be cured because he has faith whereas a sceptical one is not; one method such as suggestion may cure when analysis has failed and vice versa. The spiritual healer may succeed where the physician, particularly if untrained in the recognition and treatment of psychological illness, may fail.
>
> It is undesirable and even dangerous for anyone to apply these methods of treatment without a knowledge of the nature of the disease from which the patient is suffering. To treat certain forms of depression by laying on of hands or resort to the help of spirit media, or by suggestion, when specific treatment is available is to do the patient the greatest disservice.

[1] "Divine Healing and Co-operation Between Doctors and Clergy", memorandum of evidence submitted by a special committee of the Council of the British Medical Association to the Archbishops' Commission on Divine Healing; 1956. London: British Medical Association. 8½" x 5½", pp. 47. Price: 2s. 6d.

Organic disorders claimed to be cured by spiritual healing are discussed. Sometimes there is an apparent cure of an organic disorder, and most of these cures are said to come in one or another of the following categories: (*a*) mistakes in diagnosis, (*b*) mistakes in prognosis, (*c*) alleviation, (*d*) remission, (*e*) spontaneous cures, (*f*) combined treatment. In this section is the following paragraph:

> When all these possibilities are considered it leaves little room for miraculous cures of organic disease by methods of spiritual healing. In any event, spontaneous or unexpected cures in this country, like those of Lourdes, which cannot be explained are very few; and in the committee's opinion it is probably better to acknowledge that they are at present inexplicable on scientific grounds.

Under the heading of the religious aspects of healing the subjects discussed are conversion, suggestion, morale and other environmental factors. The general conclusion is stated in the following terms:

> To summarize, we can find no evidence that there is any type of illness cured by "spiritual healing" alone which could not have been cured by medical treatment which necessarily includes consideration of environmental factors. We find that, whilst patients suffering from psychogenic disorders may be "cured" by various methods of spiritual healing, just as they are by methods of suggestion and other forms of psychological treatment employed by doctors, we can find no evidence that organic diseases are cured solely by such means. The evidence suggests that many such cases claimed to be cured are likely to be either instances of wrong diagnosis, wrong prognosis, remission, or possibly of spontaneous cure.
>
> On the other hand, as there are multiple factors—whether of body or mind—which may contribute to the precipitation of an illness, so there are multiple factors which conduce to the restoration of health. Since man is a unity and health a condition of full functioning, we cannot afford, especially in critical illnesses, to disregard any means at our disposal which may lead to the restoration of a man's health, since all the functions of the personality react upon one another. The emotional life of an individual has a direct bearing upon his physical well-being, as everyone knows who has experienced what it is to be depressed and to be happy. Religious ministration on whatever basis it rests may have an important bearing upon the emotional and spiritual life of the patient and so contribute to recovery.

Many people will say that these "conclusions" do not carry us very far. It is difficult to see how they could do so. The upshot of the whole matter is that cooperation between doctors and clergy in the interests of the patient must be the mutual aim of medicine and the church. Doctors often declare that the clergy should learn more of disease and of what it consists. In reply to this we have previously drawn attention to the justice of the counter claim that doctors should pay more than passing attention to the teachings of the church and the ministrations of its clergy.

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## DUODENAL REGURGITATION AND THE GASTRIC MUCOSA.

THE relationship between malignant changes in cells and external carcinogenic factors is still obscure. Carcinogens act probably as irritants from which cell mutations arise and thrive as relatively resistant and hence as successful competitors in the perpetual struggle for cell survival. If specific irritants are rapidly carcinogenic it seems likely that chronic irritation over a long period of time may well in susceptible tissues also result in neoplastic and possibly malignant changes. The familiar examples of solar radiation in skin cancer, local irritation and tongue cancer, and a local infection and cancer of the cervix illustrate this point. In other cases there may be a mixture of local irritation and a specific carcinogen, and though the subject is one of much opinion and little fact, it may well be that carcinoma of the bronchus and of the stomach are of this mixed type. The whole question is extraordinarily complex and surmises skim heroically over gaps in knowledge. Perhaps in some years' time the present thoughts on the subject may seem mistaken, but at the moment workers must pursue the diligent search for truth. It has for long been held and well substantiated that chronic atrophic gastritis, as a result of chronic gastric irritation, is a precursor of malignant change. Quite apart from the irritative effect both of psychosomatic tensions and of local gastric contents, it has been suggested that there may be a specific gastric carcinogen acting on the cells of the gastric mucosa; this carcinogen may be of dietary origin. M. Siurala and M. Tawast[1] have investigated the conditions in man which could give rise to prolonged contamination of cells of the gastric mucosa, absorption of a possible carcinogen and contamination of cells in the submucosa. They suggest that in atrophic gastritis there may be found in the mucosa epithelium of the intestinal type with powers of absorption. It has been shown that water-insoluble carcinogens may be brought into aqueous solution in the presence of lipophilic-hydrophilic agents, and it is thought that these agents, though normally absent from the stomach, are brought in by the duodenal regurgitation of intestinal juice and bile. The resulting carcinogenic solution is then said to be readily absorbed by the atrophic epithelial tissue. Siurala and Tawast had as the object of their study the investigation of the coexistence in man of duodenal regurgitation and atrophic conditions of the stomach. The material consisted of 366 adults of whom 234 had gastro-duodenal abnormalities of one kind or another. Samples of morning gastric contents were taken after twelve hours' fasting. A determination of surface-lowering factors in the gastric contents was made by means of a modified Gmelin test. The sulphur sedimentation test was also carried out in 200 cases, and the absence of lipophilic-hydrophilic substances was revealed by the failure of the particles to sink within thirty seconds. All patients were examined by gastroscopy and by radiological demonstration of the state of the stomach. Gmelin-positive agents were found in the gastric contents of 18% of normal individuals and in 46% of those with severe atrophy. This highly significant statistical difference was not found between the normal individuals and those with mixed and superficial gastritis and was not significant in those patients with peptic ulcer or carcinoma of the stomach. Gmelin-positive agents were found more frequently at a pH of 6 or above. Sulphur sedimentation by surface active agents occurred in 22% of normal individuals and in 51% of those with varying degrees of mucosal atrophy. In 28 cases the result of the sulphur test was positive when the Gmelin test gave negative results, thus revealing the presence of surface-active agents other than bile. The sulphur-positive factors were more commonly present at pH 6 and above. Further investigations of the same patients and of 20 normal volunteers revealed that the results of serial examinations were consistent with the preliminary findings, though the presence of surface-active agents did vary to some extent in the same individual.

From these results Siurala and Tawant conclude that the presence of surface lowering factors is a common occurrence in the fasting gastric contents, but that this phenomenon is particularly associated with patients with atrophic gastritis and with a high pH. The results enable no firm conclusions to be drawn, though they do reveal that pre-carcinomatous conditions of the stomach are found commonly associated with the lipophilic-hydrophilic emulsifiers of potential carcinogens. These lipophilic-hydrophilic factors are also present in the diet and are sometimes added to various foods such as bread and margarine. As some combined fatty acids may themselves function as co-carcinogenic or tumour-producing agents, the further speculation along this line of thought is highly interesting.

[1] *Acta med. scandinav.*, 153: 6.

# Abstracts from Medical Literature.

## PHYSIOLOGY.

### The Role of Ascorbic Acid in Bleeding and Clotting.

J. Y. McCRAW (*Rev. canad. de biol.*, February, 1956) has studied the role of ascorbic acid in the formation of blood clots, and in the particular physiological abnormalities which occur when there is a deficiency of ascorbic acid. Numerous factors are involved, which can be separated into three main groups; these are tissue factors, cellular factors and plasmatic factors. The most important of the tissue factors is the constriction of the vessels closely related to the bleeding point. Vasoconstriction occurs because of primary nerve reflex; and secondarily following the discharge of serotin from the platelets. Any substance which increases the capillary resistance also decreases the bleeding time. A second tissue factor has been identified as the pressure of the surrounding extravascular tissues on the bleeding point. In consideration of the cellular factors, the agglutination of the thrombocytes appears to be the essential step in the hæmostatic process. The disintegration of the thrombocytes would be the primary cause of hæmostasis, due to the discharge of factors necessary, not only for thromboplastin production, but also for prothrombin activation. Other substances, equally important, would be liberated from the platelets. Thrombocytolysin enhances the agglutination and lysis of additional platelets and serotin, which, in turn, contribute to local vasoconstriction. Plasma factors involved in the physiology of spontaneous hæmostasis are consequential to the agglutination of the thrombocytes, and as a factor of reinforcement and consolidation the coagulation of fibrin increases the resistance of the clot to intravascular pressure. Production of thrombin, anterior to the fibrin clot, is, however, dependent upon the inactivation of antithrombin, whose own activity seems to be primarily regulated by the pituitary hormone. During or following stress, the bleeding time is decreased, probably through the pituitary adrenal system, and the depressing effect of cortisone-like hormones on the activity or level of antiprothrombin. The pituitary adrenal system appears to be the most important factor in the process of spontaneous hæmostasis. Although the bleeding and coagulation times are both increased during scurvy and reduced by ascorbic acid administration, it seems that the explanation of these effects should be sought in the relationship between ascorbic acid and the pituitary adrenal system. The author concludes that the chief derangement of the peripheral vascular system during scurvy appears to be one of hyporeactivity of the contractile vessels, accompanied by dilatation and slowing of the blood flow. There seems to be no change from normal in the rate of retention or of absorption of calcium either during or after the progress of scurvy in the guinea-pig. The fibrinogen content of the plasma increases sharply at the onset of scurvy. Hæmorrhage and minor degrees of infection seem to contribute but little to this increase. Scurvy is accompanied by a definite thrombocytopenia which in turn is responsible for an important decrease in thromboplastin. The author suggests that the level, and probably the activity, of the prothrombin is decreased during scurvy. This hypoprothrombinæmia, probably initiated by ascorbic acid deficiency, is undoubtedly associated with a secondary vitamin *K* deficiency. All observations made during the scurvy indicate that ascorbic acid deficiency increases symptoms of vitamin *K* deficiency. Nutritional disturbances of scurvy appear to be primarily responsible for the changes in the plasma level of total proteins, and it seems difficult to determine whether or not ascorbic acid has any influence in this respect.

### Serum Amino Acid Concentration and the Appetite.

S. M. MELLINKOFF, M. FRANKLAND, D. BOYLE AND M. GREIPEL (*J. Appl. Physiol.*, March, 1956) suggest that hunger may be related to fluctuation in amino acid metabolism. The intravenous administration of amino acid by the intravenous route may result in the cessation of gastric peristalsis and if the infusion is too rapid, anorexia and nausea appear. The authors have made laboratory measurements of the serum amino acid and blood sugar concentrations under a variety of circumstances and have attempted to make a simultaneous estimate of the appetite in the subjects. When amino acids were infused with glucose, the appetite appeared to vary inversely with both the amino acid and blood sugar concentrations, but when the amino acids were administered alone, whether by mouth or by vein, appetite appeared to vary inversely with the amino acid concentration but directly with the blood sugar. However, there was considerable variation from subject to subject. Whether induced by feeding of protein or of amino acids, or by infusing amino acid mixtures, a rise in the serum amino acid concentration appeared to be accompanied by a waning of appetite. The subsequent increase of appetite was accompanied by a fall in amino acid concentration. It was found that the administration of hydrolysed casein by the intravenous or oral route diminished appetite as the amino acid concentration rose and the blood sugar fell. Similarly, the recovery of appetite was associated with the fall in the serum amino acids and a rise in the blood sugar. The authors state that these data by no means prove that the blood sugar has nothing to do with the control of appetite. Neither do they establish a cause or relationship between the serum amino acid concentration and the appetite. It seems unlikely that the serum amino acid concentration as such is an important determinant of appetite, because the fasting amino acid concentration does not reflect the degree of hunger. Only further experiment will explain these relationships. The present observation is limited to the fact that after the consumption of protein some metabolic change associated with the waxing and waning in the serum amino acid concentration appears to affect appetite, and this effect seems to be independent of changes in the blood sugar concentration.

### Arterial Pressure Response to Infused Serotonin.

I. H. PAGE AND J. W. MCCUBBIN (*Am. J. Physiol.*, February, 1956) have found that the arterial pressure response to the intravenous infusion of serotonin in dogs and cats is usually one of a sustained fall. This differs from the usual response to a single quick injection of serotonin and suggests that the mechanisms controlling response are different depending upon the manner of administration of the drug. It is concluded that when serotonin is infused the depressor response has at least three main contributory mechanisms: (i) endogenous histamine is released by serotonin; (ii) there is peripheral inhibition of neurogenic vasoconstriction; (iii) there exists a dose-response relationship that, in some preparations, determines whether change in arterial pressure shall be a rise or fall. The response to the intravenous infusion of serotonin in three hypertensive patients was different from that in normotensive dogs and cats, or in neurogenic hypertensive dogs. The patients responded with a small, sustained rise in arterial pressure. Infusion of either histamine or serotonin in dogs caused similar changes in response to other drugs: those to DMPP were strikingly augmented and those to noradrenaline were moderately increased in both dogs and cats. Responses to angiotonin, barium chloride and "Aramine" were essentially unchanged. The depressor action of the histamine releasing drug, 48/80, or histamine, was sharply reduced or abolished.

## BIOCHEMISTRY.

### Bence-Jones Proteins.

H. F. DEUTSCH *et alii* (*J. Biol. Chem.*, September, 1955) have demonstrated that highly purified Bence-Jones proteins have immunological similarities to those of normal serum globulins. This indicates structural similarities and suggests that they may be portions of normal serum protein molecules.

### Diabetes.

C. E. FROKMAN AND J. M. OSTEN (*J. Biol. Chem.*, October, 1955) have measured the levels and the radioactivities of the acids of the tricarboxylic acid cycle in the livers of normal and alloxan-diabetic rats previously injected with acetate-1-$C^{14}$. Five minutes after injection the levels and the $C^{14}$ activities of the acids are much lower in diabetic animals than in normal controls. It is postulated that the lower counts in the cycle acids from the livers of diabetic animals result from an inhibition of some reaction necessary for the conversion of acetate to citrate.

### Cataract.

J. W. PATTERSON (*Arch. Biochem.*, September, 1955) has shown that D-xylose and L-arabinose when given simultaneously with D-galactose or in an alternating

manner with D-galactose accelerate the development of galactose cataracts. Diabetic rats fed a diet containing 20% of D-xylose develop cataracts more rapidly than control rats with diabetes on a D-xylose diet alone. Thus, D-glucose, D-galactose, D-xylose and L-arabinose are interrelated in the production of cataracts. All of these sugars have the same configuration on carbon atoms 2 and 3, and they all form a ring through carbon 1 with a resultant equilibrium of α and β forms. D-sorbitol, D-mannose and D-arabinose are non-cataractogenic.

### Hormones and Carbohydrate Metabolism.

G. E. GLOCK AND P. MCLEAN (*Biochem. J.*, November, 1955) have shown that the total levels of both glucose-6-phosphate (G 6-P) and 6-phospho-gluconate (6-PG) dehydrogenases are significantly reduced in the livers of rats maintained on restricted food intakes for eight days and also after forty-eight hours' starvation. Concentrations of both dehydrogenases are greatly reduced in alloxan diabetes, total liver activities being only approximately one-third of the control values. Thyroxine treatment results in an approximately twofold increase in the levels of activity of both dehydrogenases; whereas thiouracil treatment, although decreasing enzyme activities per gramme of liver, does not significantly affect total liver values. Although long-term treatment with crystalline growth hormone causes some increase in G 6-P dehydrogenase activity per gramme of liver, total-liver enzyme activities are not significantly affected. Liver dehydrogenase concentrations show seasonal variations and are significantly higher in summer than in winter. Crystalline insulin, crystalline growth hormone and DL-thyroxine have no in-vitro effect on either G 6-P or 6-PG dehydrogenase activity under the particular conditions employed.

### Thyroxine.

B. J. KRIPKE AND A. T. BEVER (*Arch. Biochem.*, February, 1956) have shown that thyroxine preserves the activity of succinate-cytochrome with reductase activity in preparations from rat heart homogenate, but does not increase the original activity. The preservation appears to be a chemical rather than a physical effect. At least one site of action is in the succinic dehydrogenase complex where sulphydryl groups are protected from oxidation.

### Pantothenic Acid.

B. M. TOLBERT *et alii* (*Arch. Biochem.*, February, 1956) have measured the effect of coenzyme-A on the oxidative metabolism of both normal and pantothenic acid-deficient rats. The differences in the rate of excretion of $C^{14}O_2$ show that the methyl carbon of sodium-acetate-2-$C^{14}$ is oxidized faster and in greater amount in the deficient than in the normal rats, but is slower in animals given coenzyme-A as compared to animals not given coenzyme-A. The oxidation of the methyl (omega) carbon of heptanoic acid to $C^{14}O_2$ is much more depressed by coenzyme-A than is the oxidation of the methyl carbon of acetic acid. In a confirmatory series of experiments, normal and deficient rats, with and without coenzyme-A injection, were given sodium acetate-2-$C^{14}$. Fractionation, paper chromatography and radio-autography of the livers from these rats revealed that more activity was incorporated in the liver, and especially the liver fats, in the deficient rats given coenzyme-A, than in the normal rats or deficient rats without coenzyme-A. Incorporation of radioactivity into amino acids was similar in all cases.

### Liver Catalase.

R. C. TROOP AND A. J. STANLEY (*Arch. Biochem.*, February, 1956) have demonstrated that cortisone and hydrocortisone produce a considerable reduction in rat liver catalase activity, but that there is no change in the activity of this enzyme in adrenalectomized rats maintained on sodium chloride. In their experiments, contrary to expectations, ACTH did not alter liver catalase, even in doses of six milligrammes per day. Testosterone promoted an increase of catalase activity in mature female rats but not in immature females. Castration of male rats did not alter the catalase activity to a degree that was statistically significant.

### Phenolic Acids.

M. D. ARMSTRONG *et alii* (*J. Biol. Chem.*, February, 1956) have isolated *m*-hydroxyhippuric acid from human urine. Although the amount of *m*-hydroxyhippuric acid normally found in human urine is very small, it is quantitatively one of the most important phenolic acids occurring in most samples of the urine. The amount excreted by an adult varies from two to 150 milligrammes per day, and the average excreted amount is four to six milligrammes daily. Most of the urinary *m*-hydroxyhippuric acid originates from some dietary precursor, but it is possible that a small amount may be formed endogenously.

### Cobalt.

M. T. LAFORET AND E. D. THOMAS (*J. Biol. Chem.*, February, 1956) have reported that cobalt in concentrations of $10^{-2}$ to $10^{-8}$M did not stimulate either oxygen consumption or hæmoglobin synthesis in bone marrow. Cobalt at concentrations greater than $10^{-4}$M inhibited hæmoglobin synthesis, but did not interfere with oxygen consumption until concentrations of $10^{-3}$M were reached. This was interpreted to mean that cobalt does not produce polycythæmia by a mechanism of bone marrow anoxia.

### Cell Growth.

H. EAGLE *et alii* (*J. Biol. Chem.*, February, 1956) have demonstrated that both a mouse fibroblast (L strain) and a human carcinoma cell (strain Hela) require L-glutamine for survival and growth in tissue culture. In their experiments the maximally effective concentration of L-glutamine was 0·2 to 0·5 mM for the fibroblast, and 1·0 to 2·0 mM for the carcinoma cell. The addition of a full complement of amino acids had a glutamine-sparing action, but did not affect the glutamine requirement qualitatively. Glutamic acid at the optimal concentration of 20 mM substituted for glutamine in the case of the Hela cell but not in that of the mouse fibroblast. The further addition of ammonium chloride often increased the growth response of the former cell and occasionally permitted slight growth of the latter. Arginine, ornithine, α-ketoglutaric acid and proline were inactive as substitutes for glutamine. It is suggested that glutamine is an essential metabolite under the conditions of these particular experiments and that the growth-promoting activity of high concentrations of glutamic acid for the Hela cells reflects its conversion to glutamine.

### Urobilinogen.

P. LOWRY *et alii* (*J. Biol. Chem.*, February, 1956) have described the isolation of crystalline *d*-urobilinogen. It has been obtained both from fæces of patients treated with "Aureomycin" or "Terramycin" and after brief amalgam reduction of *d*-urobilin. The *d*-urobilinogen is formed by bacterial activity, but whether it is an abnormal, or a transitory normal, intermediary compound remains to be determined.

### Pyrimidine Metabolism.

K. FINK *et alii* (*J. Biol. Chem.*, January, 1956) incubated rat liver slices with thymine and demonstrated that β-aminoisobutyric acid (BAIB) was produced slowly and without detectable accumulation of dihydrothymine (DHT) or β-ureidoisobutyric acid (BUIB), both of which were rapidly and extensively converted to BAIB when added as substrates. Conversion of BUIB to BAIB appeared to be irreversible under the conditions employed, while interconversion of BUIB and DHT was clearly detectable, and thymine appeared in the incubation media when DHT was used as substrate. No evidence was obtained for participation of BAIB amide in this series of reactions. Evidence for the following interrelationships was noted when whole animals were used:

Thymine ← dihydrothymine ⇄ β-ureidoisobutyric acid → β-aminoisobutyric acid.

With the related uracil series of compounds the reaction was clearly demonstrable *in vivo*.

### Œstrogens.

C. D. WEST *et alii* (*J. Biol. Chem.*, January, 1956) have shown that when testosterone propionate was administered to two women with metastatic breast cancer, who had undergone oophorectomy and adrenalectomy, œstrone and œstradiol-17β were identified in the urine. Neither compound could be identified in the control urine when the patients received no testosterone. In as much as both patients were castrated and adrenalectomized, it was concluded that the œstrone and œstradiol-17β originated from metabolism of the administered testosterone. Many other unidentified phenols were demonstrated in the urine during testosterone therapy. It could not be established whether testosterone was converted to œstriol.

# Clinico-Pathological Conferences.

## A CONFERENCE AT SYDNEY HOSPITAL.

A CLINICO-PATHOLOGICAL CONFERENCE was held at Sydney Hospital on November 22, 1955, PROFESSOR H. K. WARD in the chair. The principal speakers were the members of the Diabetic Clinic of Sydney Hospital.

The following clinical history was presented.

### Clinical History.

For eleven years the patient, a female, aged fifty-three years, had been treated for *diabetes mellitus*, recently with 15 units each of protamine zinc and soluble insulin daily. She had remained in good health till four days before admission to hospital, when she suffered from a shivering attack and felt that she was getting a cold. Her doctor found her febrile with signs suggestive of pneumonia at the base of the right lung and treated her with sulphathiazole tablets to a total of four grammes in the three days. On the night before her admission to hospital he gave her an injection of morphine, after which she became comatose.

On the morning of arrival in hospital she was in coma with her breath smelling strongly of acetone and her urine laden with sugar and acetone bodies. Her temperature was 102° F., pulse rate 110 per minute, blood pressure 110 millimetres of mercury, systolic, and 70 millimetres, diastolic, and there were crepitations at the base of the right lung. Her blood sugar content was 680 milligrammes per 100 millilitres and her blood urea content 135 milligrammes per 100 millilitres. A Ryle's tube was passed into the stomach, and 11 ounces of bile-stained fluid were withdrawn. She was given penicillin 15,000 units every three hours, saline and glucose fluids intravenously, "Anacardone" and 50 units of insulin four times in the first day. Blood examination in the afternoon showed 12·3 grammes of hæmoglobin per 100 millilitres, 14,000 white cells per cubic millimetre comprising 96% neutrophile cells and 4% lymphocytes, a blood sugar content of 674 milligrammes and cholesterol content of 225 milligrammes per 100 millilitres. Next morning her blood sugar content was 290 milligrammes per 100 millilitres and she was given 120 units of insulin during that day and again on the succeeding day. Her condition improved, fluids were given by mouth as well as intravenously, but her temperature remained at about 100° F.

On the fourth day her condition deteriorated. Her urinary output became very small, her blood sugar level rose to 1110 milligrammes per 100 millilitres and her blood urea content to 290 milligrammes per 100 millilitres, the carbon dioxide combining power was 15 volumes *per centum*, and she lapsed into coma. She was given sodium sulphate solution intravenously and 80 units of insulin in the day. Her urinary output remained extremely small, and she died on the sixth day. Throughout her stay in hospital she had been febrile (100° to 102° F.) and had been treated with penicillin.

### Clinical Discussion.

PROFESSOR H. K. WARD: The subject for discussion this afternoon is the death of a diabetic in coma. I call on Dr. Read to open the discussion.

DR. F. H. READ: This case which you have before you is one which seems to us in the clinic to be obscure, and it is our feeling that the afternoon could well be spent by first discussing the case as a whole and presenting our diagnosis—that will be done by Dr. Watson—and then discussing briefly the causes of diabetic coma and their diagnosis. Dr. Nagy will stress this aspect of the problem. Dr. Heselton will then outline for us the importance of establishing normal electrolyte metabolism, and finally I propose to deal with the management of diabetic coma. I will now ask Dr. Watson to deal with the case as a whole and present our diagnosis.

DR. L. C. A. WATSON: We have before us the clinical history of a female patient, fifty-three years of age, a diabetic who died in coma. I would like to commence the discussion of the case by commenting on some of the salient features. Firstly, she was a known diabetic under treatment for eleven years; that is, the diabetes was first recognized at the age of forty-two years. Secondly, immediately before her death she was having only 30 units of insulin per day; so that, if we may assume that she was reasonably stable on this dosage, she was a diabetic of only moderate severity. Thirdly, the terminal illness was of sudden onset—she is reported as being in good health only ten days before she died.

This much, the background, as it were, to her final illness seems clear and explicit, but unfortunately it is not as easy to form a clear picture of the sequence of events which comprised this illness. It was febrile throughout. It began with a rigor—the patient thought she was catching a cold—and it was associated with signs which her local doctor thought were suggestive of pneumonia at the right lung base. She was treated (quite inadequately) with eight tablets of sulphathiazole spaced over a period of three days, and on the fourth night she lapsed into coma.

When she arrived in hospital on the fifth morning of the illness, she was in diabetic coma. She was given orthodox treatment of only moderate intensity, and she recovered consciousness.

On the third day of hospitalization she seemed much better. She had been given 200 units of insulin on the first day, followed by 120 units on each of the second and third days. She was taking copious fluids by mouth and by vein, and was occasioning no real concern, even though she remained persistently febrile.

Then, on the fourth hospital day she deteriorated rapidly, and, apparently, the first feature of this deterioration was sudden severe oliguria, which persisted until her death. Her blood urea level rose; her blood sugar level rose; she was severely acidotic, and she relapsed into diabetic coma, from which this time she was not to recover. The details of her management at this stage are sketchy, but she was obviously given some fluid intravenously, and for some reason she was given less insulin on the fourth day than on any of the previous three. At any rate, her oliguria, her temperature and presumably the other features all persisted, and she died on the sixth hospital day, ten days after the beginning of the illness.

In broad outline, then, we have a moderately severe, middle-aged, female diabetic, who suddenly developed a febrile illness, which was thought to be a respiratory infection and which precipitated her into coma. After initial recovery on orthodox treatment she relapsed and died in coma with urinary suppression, having been febrile throughout. It is quite obvious that the woman died in diabetic coma. The essential diagnostic problem concerns the nature of the precipitating illness or illnesses. Now, in my opinion, the two features of the case which are most likely to afford valuable clues to diagnosis are, firstly, the persistent pyrexia which did not respond to 15,000 units of penicillin given three-hourly and, secondly, the severe oliguria.

To take the pyrexia first. There are, of course, a number of causes of pyrexia apart from infection—leuchæmia, the reticuloses, severe anæmia, carcinomatosis, the so-called collagen diseases and others. But in this case I think it is difficult to consider any other cause of pyrexia apart from the infective complications which are so common in *diabetes mellitus*.

Where may this infection have been? At first sight it would seem almost certainly respiratory in nature, but on closer examination the evidence is not really conclusive. The fever, rigor and even the symptoms of a "cold" are non-specific. There is no mention of a cough or any other definitely respiratory symptom, and the only respiratory signs to which specific reference is made are crepitations at the right lung base on admission to hospital in diabetic coma; this surely is very little on which to make a diagnosis. There is no report of a chest X-ray examination. I think it is quite probable that she did have a respiratory infection at this stage, but I also believe that it would be not unreasonable to argue that no such infection was ever present.

If it was a respiratory infection, then what type was it? It seems unlikely that a simple coccal bronchitis or bronchiolitis with or without bronchopneumonia was the only infection present. For, although the sulphathiazole treatment before admission to hospital was inadequate, I believe that the great majority of such infections responded to penicillin in that dosage, which was the usual one in those days before penicillin resistance became a major problem. If this supposition is valid, we are left with virus pneumonia, tuberculous bronchopneumonia and infections with some of the rare organisms, Friedländer's bacillus, fungi and so on. There is really no specific evidence in favour of any one of these diagnoses.

Now let us consider the proposition of an infection somewhere else. Pus in the sinuses, middle ear, uterus and adnexæ, pleural space, subphrenic space, liver, gall-bladder

and appendix, pancreatitis, subacute bacterial endocarditis, septicæmia and pyæmia are all conditions which have been known to be occult; but there is no evidence in favour of any of them apart from general suspicion in a patient such as this, who did not do well and was not very throughly investigated.

I have purposely left the kidney to last because infection in this region is a much more definite possibility and would tie up better with the second main clue, namely, urinary suppression. Urinary suppression may be pre-renal, renal or post-renal. None of the causes of post-renal (obstructive) oliguria fits the picture well, although sulphonamide crystalluria obviously requires some thought. Nevertheless, the dosage given was small, and the time relationships of the oliguria are such that I believe it can be confidently excluded. The story, as I read it, is of a woman whose fluid and electrolytes on that third day when she seemed so well were probably reasonably well adjusted. Then, fairly suddenly, the urine flow ceased; and following this she passed into coma. If this interpretation is correct, I believe that pre-renal oliguria can be regarded as improbable, unless she had on that fourth day a sudden, shocking vascular catastrophe (of which coronary occlusion would be a common example), and there is certainly no suggestion of this in the story as it stands. This leaves us with the renal causes of severe urinary suppression, and a number of these—the poisons, obstetric complications, surgical shock or instrumentation, incompatible blood transfusion, glomerulonephritis, the terminal stages of polycystic kidneys—can be excluded at once. There remain pyelonephritis, renal tuberculosis, perinephric abscess, hydronephrosis and pyonephrosis. Tuberculosis is a complication of diabetes in the renal tract as in the respiratory, and, I suppose, it is theoretically possible also that the patient had miliary tuberculosis. But as in the case of so many other conditions I have mentioned, there is no specific evidence for it.

Pyelonephritis, on the other hand, is a diagnosis which has a great deal to recommend it. It is common in diabetics, and it is a common precipitating cause of diabetic coma. It would explain the persistent fever, since few of the organisms respond to penicillin. It is usually associated with few, if any, physical signs of which there is such a dearth in this case; and it would help to explain the terminal, severe, renal involvement. It is a diagnosis which, in this case I believe, could have been made or marred by a full urinary examination including microscopy and culture, and this information is, of course, a most important omission from the history.

Even so, almost complete anuria in uncomplicated pyelonephritis, even when severe, must be uncommon. The rare but specific complication of diabetes known as necrotizing renal papillitis occasionally follows in the course of pyelonephritis in diabetics; and this condition would explain all the features of this case. It is commoner in females and very rare under the age of forty. It usually occurs as part of an acute pyelonephritis; it is commonly associated with urinary suppression, and it is highly lethal. It is a more or less specific complication of diabetes.

An excellent description of it is in the paper of Edmondson, Martin and Evans, who found papillary necrosis in 29 of 859 diabetics in a series of 32,000 autopsies. In the same series of autopsies there were 1023 non-diabetic patients with pyelonephritis, and 21 of these had papillary necrosis. In 20 of these 21, however, there was definite associated urinary obstruction. So that in this very large series of autopsies this uncommon condition was seen only fifty times. Of these patients over half were diabetics, and all but one of the remainder had definite urinary obstruction.

To summarize, the patient died in diabetic coma with urinary suppression. I think it is most likely that this resulted from acute pyelonephritis associated with necrotizing renal papillitis. It may be that the pyelonephritis was present from the beginning of the illness and was responsible for the first episode of coma. But it is just as likely that the initial coma was due to a respiratory infection, and that the urinary infection was introduced with the catheter during its management.

A second possibility is that the urinary suppression was pre-renal in origin due to severe electrolyte imbalance, and in this case the ultimate cause of her death would be a severe infection either in the lung or elsewhere.

DR. READ: I will now ask Dr. Nagy to deal with the common causes of diabetic coma.

DR. G. S. NAGY: Diabetic coma is one of the major medical emergencies.

The foregoing case history illustrates how a moderately severe diabetic woman, who was in good general health, perished in ten days after the onset of an illness which precipitated a diabetic coma. One feels that certain lessons can be learned and certain features can be stressed, using this case as an example.

Diabetic coma still carries a high rate of mortality, even in hospitals where a specialized unit deals with such admissions. Joslin gives an overall mortality rate of 8·3%, but mortality rates up to 30% or 40% are not rare in different series, depending on the severity of the cases selected in each group.

The prognosis in each individual case will depend on the severity of diabetic acidosis, duration and degree of coma before treatment is commenced, any complicating factors which are present, the state of the cardio-vascular and renal systems, and the age of the patient.

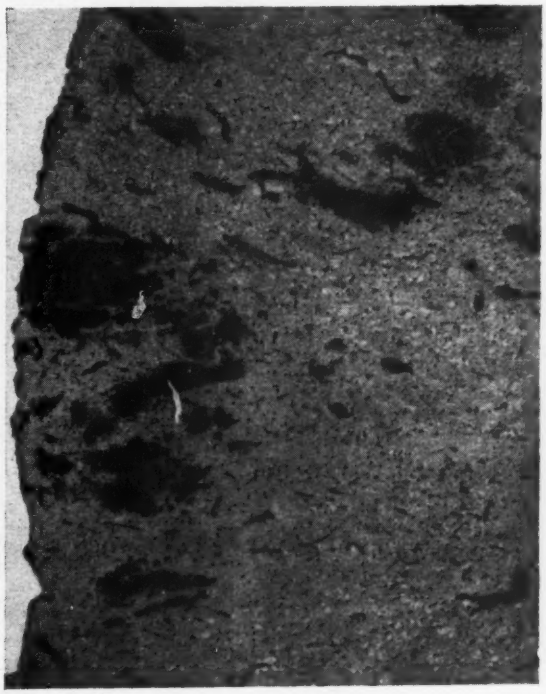

FIGURE I.

Frontal lobe of brain showing numerous petechial hæmorrhages (very low power).

Diabetic acidosis is rather insidious in its onset. Early symptoms are vague, such as headaches, malaise, nausea, vomiting and abdominal pain. Only at times may there be symptoms of uncontrolled diabetes, such as thirst and polyuria. Later with more severe acidosis the picture changes to one of drowsiness, of stupor with "air hunger" or Kussmaul breathing. The fully developed diabetic coma gives a dramatic picture of an unconscious or semiconscious patient, restless, distressed as in pain, with gross signs of dehydration and with long, deep, rapid breathing, or possibly this may be replaced by a terminal shallow respiration.

The treatment of such a patient may tax the integrated skill of the physician and biochemist. The natural tendency is to focus all attention on correcting the severe hyperglycæmia and dehydration. The prompt treatment of diabetic coma is stressed by everybody.

Nevertheless, one must not overlook other, perhaps less spectacular measures than the intravenous infusions and insulin therapy.

Concurrently, as steps are being taken to control the dehydration and hyperglycæmia, one has to ask what was the precipitating cause of the diabetic coma, and is this factor still operating and possibly abolishing the beneficial effect of an otherwise efficient treatment?

Only if these questions are adequately answered can one effectively deal with the diabetic coma. At times the condition that brought on the coma cannot be removed or treated, as may possibly have been the case in the patient under discussion; these are the people who more often than not die in spite of all efforts.

Our patient presented with a febrile illness and lapsed into coma. At first she appeared to respond adequately to the treatment directed to combat the ketosis, but the pyrexia persisted, and apparently no successful investigations were undertaken to establish its cause; therefore there was no specific treatment to deal with this problem. Under these circumstances the patient once again passed into a coma, more severe than the previous one, did not respond to further measures of resuscitation and died two days later.

Fortunately, in the vast majority of cases of diabetic coma the precipitating cause is relatively easy to establish. We

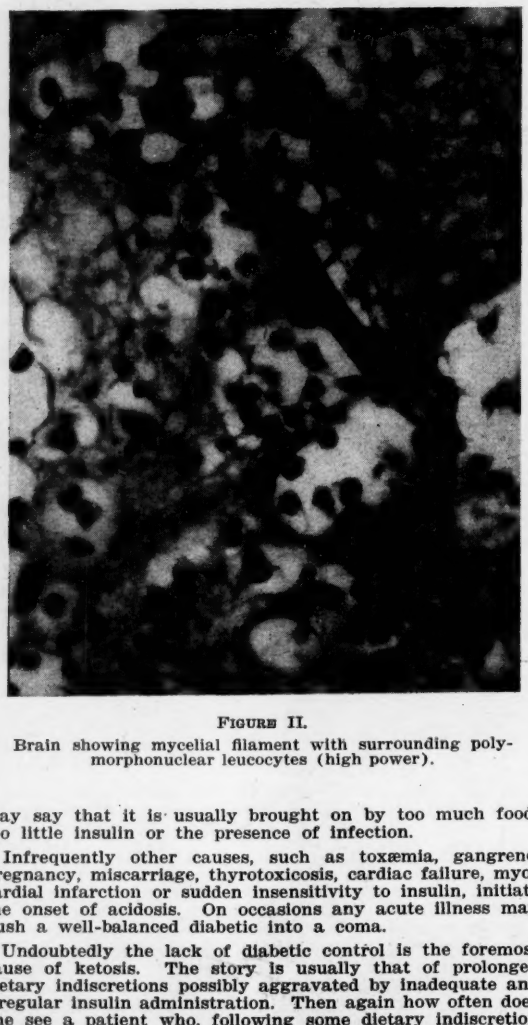

FIGURE II.

Brain showing mycelial filament with surrounding polymorphonuclear leucocytes (high power).

may say that it is usually brought on by too much food, too little insulin or the presence of infection.

Infrequently other causes, such as toxæmia, gangrene, pregnancy, miscarriage, thyrotoxicosis, cardiac failure, myocardial infarction or sudden insensitivity to insulin, initiate the onset of acidosis. On occasions any acute illness may push a well-balanced diabetic into a coma.

Undoubtedly the lack of diabetic control is the foremost cause of ketosis. The story is usually that of prolonged dietary indiscretions possibly aggravated by inadequate and irregular insulin administration. Then again how often does one see a patient who, following some dietary indiscretion or drinking bout, develops a gastritis with anorexia and vomiting, stops eating and therefore omits insulin and in such way starts off the sequence of events leading to diabetic acidosis?

Infections, of course, play an important part in the causation of diabetic coma—important, not only because it is a frequent factor in the production of ketosis, but also because if undetected and untreated it may tip the scales against the chances of the patient's recovery. Nowadays, in the antibiotics era, when infection can successfully be dealt with, it is even more essential to recognize such ætiological factors.

Deep and superficial pyogenic infections, respiratory, gastro-intestinal and renal tract infections are the commonest types associated with ketosis. Pancreatitis and hepatitis or appendicitis may be incriminated at times. Acute surgical conditions such as the latter have to be dealt with in spite of ketosis. Naturally any other infections, such as meningitis *et cetera*, may be a causative factor.

To sum up, the need for thorough and searching physical examination is essential. One has to be satisfied that there is no infection in the sinuses, ears or respiratory tract. Subcutaneous or perinephric abscesses must not be missed. The urine must be examined for pus cells and cultured repeatedly, remembering that pyelonephritis is not infrequently an ætiological factor. As we are dealing with diabetics, one must not omit to think of tuberculosis as a possible cause of ketosis. We must remember that in diabetic coma the temperature is normal or even subnormal; therefore pyrexia, particularly if persisting, must be accounted for.

I hope to be forgiven if I have so emphatically, and may be lengthily, stressed the obvious point, that the treatment of diabetic coma commences by establishing the precipitating cause and adequately dealing with it to eliminate its effect if possible.

DR. READ: I do not think Dr. Nagy need apologize for expressing so clearly one of the most important things in the management of electrolyte imbalance.

DR. T. W. HESELTON: You have just heard emphasized the importance of the role of acidosis in the production of diabetic coma. The very nature of this acidosis produces profound changes, both in the volume relationships and in the electrolyte balance or electrolyte composition of the internal environment, both the extracellular fluid and the intracellular compartment. And it cannot be emphasized too strongly that if diabetic coma is to be adequately and efficiently managed, a knowledge of the physico-chemical factors in the internal environment is a most important thing.

The sole contribution we have with respect to this unfortunate patient under discussion is the fact that she had a carbon dioxide combining power of 15 volumes *per centum*, which is 6·8 milliequivalents per litre. There is no mention of sodium, potassium or chloride; so that anyone who had the misfortune of endeavouring to treat this patient would be very much uphill. I have put on the blackboard the normal values for some of the important biochemical factors, and I have indicated the changes found in diabetic coma. The whole electrolyte disturbance is based on the production of an uncompensated metabolic acidosis, which arises from two salient features. The first is an elevation of the blood sugar level due to a disturbance of the metabolic pathway of fat or carbohydrate or both, which I do not propose to attempt to discuss here. The second is the overproduction of ketone bodies, the chief ones being the keto-acids and especially, I believe, the enolic form of diacetic acid, which is alleged to be the one which is most toxic to the metabolism of the cell as a whole.

The chain of events which takes place in the production of this acidosis is simply this. In the initial stages of coma one has an overproduction of keto-acids, which cause absorption and lowering of the plasma sodium and a depletion of water in the extracellular fluid, which, of course, then affects the intracellular compartment, as you well know. With regard to chloride, it is lost in urine and also in the vomitus. Another cause of loss of fixed base, which I do not think operates here, is loss of secretion of the upper small intestine with consequent carbon dioxide retention, causing alkalosis and diuresis with loss of fixed base in that way. The loss of fixed base in the urine results in a temporary alteration of pH. The compensatory mechanisms are largely due to the respiratory buffers of the blood governed by the Henderson-Hesselback equation. Later all buffers fail, and the picture of an uncompensated metabolic acidosis supervenes.

With regard to the carbon dioxide combining power, Joslin states that in the pre-insulin days he used it to distinguish between patients who were likely to recover and those who would not. When it was nine milliequivalents or less per litre, the patients perished: when higher, recovery sometimes occurred. Perhaps the physicians would care to comment on this.

The only other point I would like to comment on is potassium. Potassium rises in the plasma in the initial stages of coma for two reasons: firstly, because there is

usually a negative nitrogen balance resulting from excessive breakdown of protein, and this takes potassium as well as phosphate out of cells into plasma. The second factor which sometimes operates is that of urinary suppression, which also causes an elevation of the plasma potassium level. There is a temporary, not very high, rise, perhaps six milliequivalents per litre. Later on, when fluids are being administered, the plasma is diluted, and the concentration of potassium falls somewhat. When insulin is given, instead of glycolysis being the order of the day, glycogen is being deposited in the cells carrying with it some potassium. Later, if diuresis occurs, some potassium will be lost from the plasma causing a further lowering of concentration. So low does the concentration sometimes become that it is said by some to cause hypokalæmia and even cardiac arrest.

DR. READ: Two important points have been emphasized already—the question of diagnosis and the state of the electrolytes. I wish briefly to add these points—the management of diabetic coma, the giving of early and adequate doses of insulin, the rehydration of the patient and, with it, the elimination of ketosis and the restoration of electrolyte balance.

In theory the treatment works out very well. You simply give insulin to reduce the sugar, salt and water to cope with dehydration, the deficit of sodium and chloride and to reestablish urinary flow, and the ketosis and carbon dioxide combining power tend automatically to correct themselves. Potassium has a law unto itself. In practice, however, there is no hard and fast rule about the management of diabetic coma, and for that reason I do not propose to recommend any rule-of-thumb schedule. But you must give big doses of insulin early, preferably before admission to hospital. Some of it can be given intravenously, but, in my experience, not all of it. At our clinic we feel that perhaps two-fifths of the initial dose, whether of 100 or 200 units of ordinary insulin, should be given intravenously and the remainder intramuscularly or hypodermically. Intravenous insulin seems to be used up so quickly that it seems often to have little effect. Cooperation between the department of biochemistry and the clinician is extremely important. You cannot manage a case of diabetic coma without knowing what the blood sugar content is on admission and at least hourly, or perhaps more often in children, until there is some measure of control of the blood sugar. Other estimations of anions in the plasma must be done as required. And I am sure that all biochemists realize that they are not asked to do these tests just for the fun of it.

Occasionally these patients are admitted in shock, and it is our feeling that nor-adrenaline should be used to cope with this. As for alkali, many do not give it at all. We feel it is probably useful and, generally, after rehydration has proceeded for an hour or so, in which time the patient has had perhaps two litres of saline, we give half a litre of lactate, one-sixth normal sodium lactate. Potassium is important. I am sure many people have died in diabetic coma because of hypopotassæmia. The effects of potassium changes on the electrocardiogram are these. In the first case with a raised potassium level of 7·7 milliequivalents per litre, there is a normal *Q-T* interval, but an abnormally high, peaked *T* wave. In the other, with 3·1 milliequivalents, which is not far below normal, there is depression and later inversion of the *T* wave with prolongation of the *Q-T* interval. It is well worth while using the cardiograph on admission: it may show an infarction, hitherto unsuspected, and it will be of value in the following progress with relation to potassium.

When should sugar be given? This is a very brief review, but I am touching on points which I think are worth discussion. One has seen a patient in pre-coma with a blood sugar content of 1600 milligrammes *per centum*, and we have all seen severe coma with perhaps 600 milligrammes. It is obvious that sugar should be given when it is needed: as an arbitrary figure, begin glucose intravenously when the blood sugar level has fallen below 300 milligrammes *per centum*. Again, this is particularly important in the management of diabetic coma in children.

PROFESSOR WARD: Would you care to comment, Dr. Isbister?

DR. J. ISBISTER: I should like to thank the three speakers for their masterly discussion, and in the short time at my disposal I should like to make a few remarks, some of which will be against what has been said regarding electrolytes. This patient apparently was treated for a few days at home during the early part of her infection without any increased dose of insulin. I think that is probably why she went into coma in the first instance. It has been my experience that a number of doctors feel that if the patient is not eating very well, maybe vomiting, the correct thing to do is to reduce the dose of insulin, because they are afraid of the patient going into hypoglycæmia. I think that is one of the common causes of diabetic coma these days—the doctor or the patient reducing the dose of insulin because the patient is not eating very well. I think the patient went into coma the second time because of continuing severe infection, but also because of inadequate doses of insulin. I would now like to make a few remarks about the biochemical control. It has been pointed out that it is absolutely essential to have blood sugar and electrolytes estimated regularly for the control of diabetic coma. I entirely agree that that is desirable, but at how many places in New South Wales can this be carried out?—probably not more than three or four. Many of these cases of coma can be treated successfully in the country, where it is impossible to carry out these estimations three or four times a day. I feel that there are very few severe diabetic comas which cannot be treated well on clinical grounds. We have all had to treat diabetic coma by clinical judgement and with urine tests for sugar. I feel with the combination of these two things we can manage diabetic coma well in most instances. I think the treatment of some of these patients, as Professor Platt said, cosmetically, is not altogether a good thing and may sometimes get us into error through giving too much of something. Clinical judgement can add a lot to the treatment of these cases.

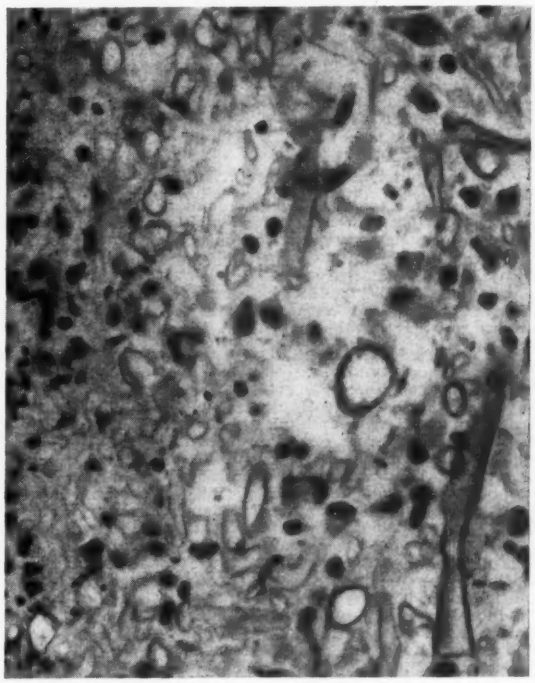

FIGURE III.

Numerous mycelial filaments in lung abscess, which in this situation is actually a dilated bronchus (high power).

PROFESSOR WARD: Thank you. Dr. Harrison?

DR. K. S. HARRISON: I have been very interested to hear the presentation of this case. I do not know the answer, but I certainly agree with Dr. Watson's discussion of it, which was masterly, and it would seem to be a case of papillary necrosis. We have seen two in the last two or three years. Both presented in a rather similar fashion with fulminating infection together with coma in one case and mild acidosis in the other. I fear that if we started a debate on the treatment of diabetic coma we would be here till this time tomorrow, as it is a very fruitful source of differences of opinion. Perhaps I should just say what I think, though probably no one else will agree. We have suggested at Prince Alfred Hospital that those cases in which the diagnosis is certain should receive 100 units of insulin intravenously and 100 units intramuscularly in casualty. Then they should be started on an intravenous drip, and we think they should have fluid corresponding to the extra-

cellular fluid—that is, Nabarro's fluid, or one bottle of lactate to two of saline. Most of us consider it is safe to give potassium routinely after the third or fourth hour, and also, I think, extra water should be given at that time. If only saline or similar fluids are given, then none of the cellular water is replaced and the cells remain dry. So after about the fourth hour it is usually safe, if the urinary output is adequate, to give potassium and, in a side drip, one-fifth normal saline and 4% glucose. Of course, this scheme may need to be varied, and it is very wrong to have a rigid routine treatment.

I would agree with Dr. Isbister that these people can be treated in a humpy or in an outback town controlled only by urine tests, but I do think they can be treated better when full biochemical facilities are available. I do not think clinical judgement need be confused by the extra information. Throughout the work where all the biochemical facilities are used in the management of diabetic coma, the series show a greater proportion of living patients.

PROFESSOR WARD: Thank you. Dr. Robertson, would you care to comment?

DR. S. E. J. ROBERTSON: I can add nothing to the discussion on the cause of death in this patient. My own experience in diabetic coma is entirely confined to children, and I would like to add a few remarks on the treatment of coma in this age group. Firstly, the child in coma is a much easier problem as there are never any degenerative vascular, nervous or renal complications. Secondly, the parents seek medical attention earlier, and stupor or coma has rarely been present for long before treatment is started. Thirdly, coma is rare in the treated child diabetic, and most cases in my experience have been at the onset of the disease. The last point is important, and urine testing must be done early in any case of coma. Such children often have a stiff neck, lumbar puncture is usually performed first, and it is a little embarrassing if the pathologist makes the diagnosis by reporting a high level of sugar in the cerebro-spinal fluid.

With regard to treatment, I agree with Dr. Harrison that biochemical determinations can be a great help. Blood sugar contents should be estimated every three hours till they have reached a satisfactory level. A child admitted in coma should be alert and taking fluids by mouth in six to twelve hours. Heroic repeated doses of insulin, as used in adults, are not advisable. The initial dose is two units per kilogram of body weight, and nothing further is given for six hours, and then according to the response of the blood sugar. Repeated doses more frequently are very likely to cause severe hypoglycæmia. Restoration of body fluids and electrolytes is the most essential point of treatment, and if carefully and rapidly performed little insulin is necessary. We have been using intravenous fructose recently as a 5% solution mixed with equal quantities of isotonic saline as the initial infusion, but have found results no better than with isotonic saline used alone. Potassium in the form of dipotassium hydrogen phosphate is used from the onset in the normal daily requirement, depending on the patient's weight. The amount of fluid is twice the child's daily requirement, about 150 cubic centimetres per pound. Sodium is given as sodium chloride and bicarbonate. The total sodium required is about three times the normal daily requirement in the first twenty-four hours. Sodium in the form of the bicarbonate is added to the solution, usually about one milliequivalent per pound, depending on the level of serum bicarbonate.

### Autopsy Report.

Slides were shown and the following autopsy report was given by DR. A. A. PALMER.

The body was that of a middle-aged female.

Pleural cavities. There was slight excess of free fluid in both pleural cavities.

Right lung. Several well-defined round, pale brown regions were present in the middle and lower lobes. The overlying pleura was congested. Near one of these regions a vessel containing firm thrombus was found. The lesions measured one to three centimetres in diameter. There was some œdema of the rest of the lung.

Left lung. This showed the same features as the right lung. Three lesions were present.

Spleen. The spleen was enlarged to about twice its normal size. The cut surface was soft and congested, and there were a few small pale infarcts.

Right kidney. In the adipose tissue near the capsule there was a dark brown semifluid lesion one centimetre in diameter resembling an abscess. The kidney was not involved but showed some congestion.

Left kidney. This showed only congestion.

Pancreas and adrenals. No abnormality found.

Brain. On the medial surface of the anterior pole of each frontal lobe there was an area of congestion with underlying petechial hæmorrhages and some softening. Numerous conspicuous petechial hæmorrhages were present throughout both cerebral hemispheres and in the brain-stem and pons.

*Microscopic Examination:*

Brain. In the frontal lobe there is acute hæmorrhagic meningo-encephalitis. Fragments of branching non-septate mycelium are present in the walls of the blood vessels and in the grey and white matter. Many are surrounded with well-preserved polymorphonuclear leucocytes indicating that the infection occurred during life and was of short duration. In other parts of the brain there are petechial hæmorrhages but no mycelium.

Lung. In the lesions described above there is profuse growth of mycelium similar to that in the brain with accompanying acute inflammation and hæmorrhage. Some nearby vessels are thrombosed, and fragments of mycelium are present in the clot and in the vessel wall.

Right eye. Many of the small vessels of the sclera are thrombosed, and mycelium is present in the vessel wall and in the clot.

Pancreas. The islets show no histological abnormality.

### Diagnosis.

1. *Diabetes mellitus.*

2. Mucormycosis involving the brain, eye, lungs and possibly the perirenal adipose tissue.

The diagnosis of mucormycosis was based on the characteristic appearance of the large branching hyphæ with infrequent or absent septa and showing a marked tendency to invade blood vessel walls and grow within their lumina.

Mucormycosis involving the central nervous system in man has been described in a number of cases of uncontrolled diabetes. Associated involvement of the lung and of the orbit and eye has also been recorded.

## British Medical Association News.

### SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held on April 18, 1956, at the Medical Society Hall, 426 Albert Street, East Melbourne. DR. GEORGE SWINBURNE, the President, in the chair.

### Syme Memorial Lecture.

Dr. George Swinburne introduced DR. C. J. O. BROWN, who delivered the tenth triennial Syme Memorial Lecture. He said that Sir George Syme had died in 1929, some twenty-seven years earlier; he distinctly remembered, though a careless, light-hearted fifth-year student before the great depression had hit the unsuspecting world, the gloom and feeling of sorrow and loss which spread over the city of Melbourne and the medical profession of Victoria in particular. At the time he knew that Sir George Syme was a great man, but was blissfully ignorant of his tremendous stature in the medical profession and in the State. As a new generation had grown up, Dr. Swinburne felt that it was not inopportune to recall briefly some of the life and times of the man whose memory was so justly preserved in the triennial lectureship. He particularly wished to welcome to the gathering Sir George Syme's son, Dr. Robert Syme, and his grandson Graham.

Dr. Swinburne went on to say that George Adlington Syme was born in Nottingham, England, in 1859. His father brought him to Australia when he was four years old. In 1877 he matriculated at Wesley College, winning an exhibition (for which performance the school was given a half-holiday). He took an honours course in the Melbourne Medical School, and in 1881, his final year, he secured first-class honours in surgery and medicine and an exhibition. He was resident medical officer at the Melbourne Hospital in 1882. In 1883 he went to King's College Hospital, London, and took the diploma of Membership of the Royal College

of Surgeons. To broaden his outlook he served as clinical assistant at the Royal Ophthalmic Hospital, Moorfields, at the Central London Throat and Ear Hospital, and at the Soho Hospital for Women. He took his Fellowship of the Royal College of Surgeons of England in 1885. In 1887 he returned to Melbourne and obtained his degree of Master of Surgery in 1888. He became surgeon to out-patients at the Melbourne Hospital in 1887, and in 1903 he became surgeon to in-patients; he retired in 1919 and became consultant surgeon. In 1887 he became a demonstrator in anatomy and later lecturer, a position which he held until 1905, a period of eighteen years. In 1888 he was secretary (Harry Brookes Allen was president) of the Royal Commission to inquire into the sanitary condition of the city of Melbourne—he was then aged twenty-nine years. In 1889 he was appointed police surgeon, a post he held for the remainder of his active surgical life. Other posts he held for a time in the latter part of last century were those of honorary surgeon to Saint Vincent's Hospital, honorary surgeon to Queen Victoria hospital, consulting surgeon to the Melbourne Dental Hospital and pathologist to the Women's Hospital. He became a member of the Faculty of Medicine in 1906, and a member of the University Council in 1912.

Dr. Swinburne then said that in 1908 Sir George Syme became president of the Victorian Branch of the British Medical Association, having been elected to the Council in 1897. He was instrumental in bringing about the amalgamation of the Victorian Branch of the British Medical Association with the Medical Society of Victoria, which had been a separate body since its inception in 1846. That was a master stroke, as there had not been a single State voice for the profession before that. He finally became one of the trustees of the Medical Society of Victoria. In 1912 he was appointed one of the original members as Victorian representative on the Federal Committee of the British Medical Association in Australia, the forerunner of the present Federal Council, and was elected vice-chairman. In 1914 he was one of the first to enlist, and was officer commanding the surgical staff of the Number 1 Australian General Hospital. He saw service at Gallipoli and for a time was senior surgeon on the hospital ship *Gascon*. He became very ill with an infected hand and arm and very nearly lost his life, and even when that danger was past he feared that his surgical career had ended; but after two or three years he regained the full use of his hand and his manual dexterity. In 1919 he was appointed as one of the original members of the Medical Advisory Committee of the Repatriation Commission and carried out an immense amount of work in this capacity (attending over 400 meetings), as well as being consultant surgeon to the Repatriation Department at Caulfield. In 1919 he was president of the Victorian Branch of the British Medical Association for the second time, at the height of the dispute with the friendly societies which culminated in the Wasley Award and the old capitation system, and his wise handling of the parties played a big part in settling the dispute. In 1923 he held the three chief offices of the medical profession in the Commonwealth: he was chosen as president of the First Session of the newly formed Australasian Medical Congress (British Medical Association) held in Melbourne that year; he became chairman of the Federal Committee of the British Medical Association in succession to the original holder of that office, William Hayward; and he was made a vice-president of the Parent Association in Great Britain. In 1924 he was one of three nominees of the Federal Government (and chairman) to a Royal Commission on health, many of the recommendations of which have since been adopted.

In June, 1924, Sir George Syme announced that he had retired from active surgical practice. The Victorian Branch of the British Medical Association determined to establish a foundation to mark the appreciation of the medical profession of his tremendous services to surgery, to the profession and to the community. Ultimately the foundation took the form of a triennial lectureship. A life-size portrait in oils was painted by Mr. (later Sir John) Longstaff; it now hung in a place of honour in the Medical Society Hall as a perpetual reminder of a great leader, an ideal surgeon for future generations of medical practitioners to regard and emulate. About the same time he was created a Knight of the Most Excellent Order of the British Empire.

Dr. Swinburne then said that one might have thought that such a man could rest on his oars, but not so; he took a prominent part in the foundation of the Royal Australasian College of Surgeons, first called the College of Surgeons of Australasia. The idea was not his; he had at first to be persuaded that the institution of the new body would not weaken the power and authority of the British Medical Association, on which he had imposed his faith. But after he was convinced that the science and practice of surgery would be raised by this new instrument and that it could exist peacefully and usefully side by side with the British Medical Association, he threw his whole being into the work and met without flinching the scathing criticism and bitter attacks of some of the opponents of the College. He became the first president of the College in 1927, and lived to see it gain recognition throughout the Empire and the English-speaking world. In 1928 he attended the annual meeting of the British Medical Association at Cardiff, where the honorary degree of doctor of laws of the University of Wales was conferred upon him. Earlier he had also been made an Honorary Fellow of the American College of Surgeons. He continued to serve the community and the medical profession until Saturday, April 18, 1929, when, after a meeting of the Federal Committee that week and a Chancellor's reception at the university that afternoon, in order to keep faith he attended a University Association Commencement Dinner, after having had a warning at 6 p.m. He had to be taken home, and died from a cerebral vascular accident next day. He at least passed on quickly while his mental powers were unimpaired, as he deserved after such a fruitful life. On Sunday, May 12, 1929, a special meeting of the Victorian Branch of the British Medical Association was held in the Medical Society Hall, to pay homage to his memory, at which many distinguished members of the community were present; to quote from the motion moved by the president, Dr. B. T. Zwar: "In grateful recognition of the profound and enduring service which he so unselfishly rendered to the whole medical profession of Australasia throughout his long medical career."

Dr. Swinburne, in conclusion, said that he had given an outline of George Adlington Syme's career; but every person present could read between the lines, and knew what intellect, ability and labour, and what service to fellow men, must have filled in the gaps to make such a brilliant record and to move his contemporaries to set up a memorial triennial lectureship in perpetuity. Dr. Swinburne then presented Dr. C. J. O. Brown as the tenth Syme Memorial lecturer.

*Surgery of the Heart.*

DR. C. J. O. BROWN delivered his lecture on "Surgery of the Heart, Past, Present and Future" (see page 1).

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A MEETING of the New South Wales Branch of the British Medical Association was held at Sydney Hospital on September 22, 1955. The meeting took the form of a series of clinical demonstrations by members of the medical and surgical staffs of the hospital.

### Asymptomatic Small Round Lesions in the Lung.

DR. M. FEILD DECK presented two patients each of whom had had a rounded shadow in the lung.

The first was a woman, aged sixty-one years, who had been found on mass X-ray survey to have a lesion in the upper lobe of the left lung. There were no symptoms and the results of all investigations were within normal limits. Because of the age of the patient, a peripheral bronchogenic carcinoma could not be excluded. Exploratory thoracotomy was recommended to confirm the diagnosis.

The second patient was a woman, aged forty-six years, who had been followed in the pulmonary clinic since 1939. An X-ray examination of the chest showed a rounded lesion in the left mid-zone; its appearance had not altered between 1939 and 1955. The patient had had several small hæmoptyses during that time. Investigation, including bronchoscopy, revealed no abnormality. She was subjected to thoracotomy after the date of the clinical meeting, and the tumour proved to be a hamartoma. The patient made an uneventful recovery.

DR. LYAL WATSON showed a patient with multiple secondary deposits in the lung which had presented as a symptomless rounded opacity at the right lung base. In December, 1953, the patient, then aged thirty-eight years, had become worried about a melanoma on his left posterior thoracic region, which enlarged, ulcerated and bled. It was excised widely, and histological examination showed it to be malignant. He was then well and unconcerned until November, 1954, when a routine chest X-ray examination showed a rounded lesion at the right lung base. The results of all tests performed at that time were normal, except the leucocyte count, which showed 14,000 cells per cubic millimetre with a normal differential count. Subsequent blood examinations during the next nine months showed similar counts. During those

nine months the patient continued to look and feel well and gained some weight, but the radiological opacity at the lung base increased greatly in size, and other opacities appeared at both lung bases. In September, 1955, the patient still felt well and had no abnormal physical signs. He was regarded as having multiple pulmonary secondary deposits from a malignant melanoma.

DR. J. RAFTOS presented a patient who was probably suffering from tuberculoma. The patient was a young woman, aged nineteen years, who had commenced nursing in 1953. The results of X-ray examination of the chest were normal and the Mantoux reaction was negative. In March, 1954, the patient developed a dry cough. The X-ray examination now showed a faint opacity in the right mid-zone. The Mantoux reaction was now positive. The patient's general health was good, and she continued nursing. In May, 1955, she was examined again because of cough, which was thought to be due to chronic pharyngo-tracheitis due to smoking. X-ray examination now showed a rounded opacity in the right mid-zone. The results of all investigations were normal. A tomogram showed that the lesion was solid and there was no evidence of cavitation. The patient had gained weight and now felt well.

DR. JOHN SEVIER presented a single woman, aged twenty-nine years, who had been born in Scotland, and had been resident in Australia for twenty-eight years. She was referred for investigation of a left lower lobe lesion, after routine chest X-ray examination in April, 1955. The report had read: "Rounded opacity at base of left lung. ? T.B." The following report was made on a tomogram in May, 1955: "Tumour is solid. It lies very close to the surface of the lung laterally." A provisional diagnosis of tuberculoma was made. The result of sputum examination was negative for acid-fast bacilli. The blood count and sedimentation rate were within normal limits. The results of Wassermann, Casoni and hydatid complement deviation tests were negative. The Mantoux reaction was positive. In May, 1954, a tuberculous cervical lymph node had been excised from the right side of her neck. The findings on microscopic examination were consistent with tuberculosis, but acid-fast bacilli were not found. In July, 1955, segmental resection was carried out by Dr. M. P. Susman. The histological appearance was consistent with a caseous tuberculous lesion, and direct smear examination showed a moderate number of acid-fast bacilli present. Streptomycin, PAS and iso-nicotinic acid hydrazole were administered, and post-operative progress was uneventful.

### Sex Problems.

DR. I. A. LISTWAN showed two patients with sex problems.

The first patient had presented himself primarily with a request to be castrated. He insisted on having a mutilating operation performed. The reasons he gave were that he felt a progressive change to womanhood, and that the operation would accelerate it. He had already consulted several surgeons, who had refused to cooperate. He threatened that in case of further refusals he might mutilate himself.

The patient had married at the age of twenty-nine years, had four children and had stopped sexual relations three years prior to seeking advice, because they were distasteful to both partners. His wife was always frigid and agreed to it gladly. The patient had had no erection and no wet dreams for the past three years.

There were a few points to be stressed from his family history. The patient had been more attached to his sister than to his brother, who bullied him. In toys he had preferred a golliwog and dolls and had not been interested in mechanical toys. He had also been interested in cooking and sewing, and had once made a suit for himself. His hair was fair and very wavy. When at school, he had had a soprano voice and taken part in plays in feminine roles. He had stayed clear of fights at school. At present he was more at home in the presence of women, and he was repulsed by men. He looked at marriage as a necessity. He let the hair on his head grow as long as possible and always shaved the hair on his body. He experienced pain in the genitals when in trousers.

No abnormalities were detected on physical examination. His genitals were normally developed, and he had male secondary sexual characteristics. On mental examination, although his mental functions were preserved, the results of reality testing were inadequate, and he had no insight into his condition. His emotional responses were inadequate when he discussed his problems.

Dr. Listwan said that the patient was undoubtedly of an intersexual type with feminine trends of mind and male trends in his physical and genital build. As long as his potency was maintained, it screened his homosexual longings, and he was able to engage in socially more acceptable heterosexual activities. With diminished potency the old drive reappeared, and he attempted to realize his delusional phantasies; they took the form of a psychotic reaction. As his personality was not shattered, and he still had preserved social instincts and respect for taboos, the approach to his problem seemed to point in the following directions: (i) Sublimation of his urges towards useful social activities; a typical example was his occupational conversion from a carpenter to a toymaker. (ii) Explanation of physiological facts, particularly that by removal of the male gonads he could not stimulate the growth of the female ones. (iii) The use of stilbœstrol for the purpose of developing pseudo-female secondary characteristics to give him at least some satisfaction for his cravings. (iv) Leucotomy, should the patient become more obsessed with his delusions and disorganized.

The second patient had committed offences against decency on several occasions, exposing himself to children and teenagers. The acts were usually preceded by a period of depression. The patient came from a family of eight. His father, who was a violently tempered man, had kept his children under his domineering influence and had not allowed normal social relations. The patient had run away at the age of fifteen years and was living a nomadic life. At twenty-five years he had gone to Malaya and suffered a shelling. He was also under heavy barrage in Singapore. When he returned home, his behaviour became uncontrollable. His first wife left him during the war. His second wife was ten years older than he. He was always a person of extreme instability, with lack of ability to control himself. His basic mood was circular. He had all his life had bouts of depression, alternating with elation. Those bouts of depression caused him to seek refuge in drink and irresponsible actions.

Dr. Listwan said that undoubtedly they were dealing with a psychopathic personality. The patient's whole approach to life problems and instability in major decisions would point to it, and as well as the fact that he never learnt from his experiences. However, there was also an element of depression, as evidenced by his tendency to circular moods and attacks of depression associated with drinking and alcoholism. In such cases the sexual perversion was only a symptom of a personality disorganized also in other fields. The management therefore should aim at: (i) fighting the depressive state by routine measures, like hospitalization, electroconvulsive treatment and use of stimulants and mild sedatives, (ii) reeducation to help the patient to acquire social and moral standards and to be able to control his actions better, and (iii) administration of stilbœstrol to produce a temporary pharmacological sterilization and to act as an emergency inhibition of his increased or falsely directed sexual urges.

#### *The Use of Stilbœstrol.*

Dr. Listwan said that stilbœstrol had been used in the two demonstrated cases for different purposes. In the first case it was used for purely psychological reasons: to bring the patient's delusions nearer to reality. That was achieved by causing overgrowth of the breasts and development of other heterosexual characteristics. In that way an attempt was made to compromise with his psychotic urge to self-destruction. In the second case it was used for physiological and pharmacological reasons: to cause temporary sterilization and lessening of libidinous urges. Stilbœstrol caused mild degenerative changes in testicular cells that abolished sexual desire completely. It returned within a few weeks of cessation of medication. Stilbœstrol could be taken indefinitely for such purposes.

### Hysterical Tremor.

DR. B. H. PETERSON showed a male patient, aged forty-one years, who was married and Polish in origin. He had been first interviewed at the psychiatric out-patient department on June 1, 1955. He complained of tremor of the right forearm and hand, present on attempts at purposive movements. It prevented him from working or shaving, and made dressing and eating very difficult. It had first been noticed five months earlier, while he was working on a grinding machine, on which he was obliged to push a lever repeatedly and with considerable force. He had been working on that machine for five months prior to the commencement of tremor. First, he had noticed "jitteriness" in the right hand after work; then tremor developed during work and finally spread to other tasks as well. He had had to cease work in April, 1955, and had been investigated at another hospital. After full neurological investigation he

was diagnosed as having hysterical tremor. An attempt at hypnosis was unsuccessful, but he obtained several hours' complete relief after "Pentothal" narcoanalysis. On examination at Sydney Hospital he had a marked "intention" tremor of the right forearm and hand, but no other abnormal signs could be elicited in the nervous system or optic fundi. He was receiving workers' compensation. He said that he had been educated in Poland and had studied law for two years, but had come to Australia in 1939 because of the threat of war. During the war he had served in the Militia and later in an aircraft factory. Then he married and established a photographic studio in Melbourne. In 1954 the family moved to Sydney to be near his wife's relatives, and he was forced to enter his present employment to earn a living, though he did not like it, the job being monotonous and boring to him. His own parents had been killed by the Germans during the war. Treatment consisted of several psychotherapeutic sessions, during which he gained some insight into the emotional factors involved, and physiotherapy, occupational therapy and administration of "Myanesin". He had improved slowly, though he had been hypochondriacal at times. Dr. Peterson said that it was interesting that improvement was accelerated when compensation payments were stopped, and he was now doing light work. The condition was regarded as a functional occupation tremor, but it was proposed to keep him under supervision for some time to exclude the possibility of disseminated sclerosis.

### Colectomy for Familial Polyposis.

DR. T. E. WILSON showed a married woman, aged twenty-four years, who had undergone colectomy for familial polyposis. She had had one child who had died of a hepatoblastoma. One of her sisters had had familial polyposis and carcinoma of the rectum; one other sister and three brothers were alive and well. She was in good general condition, but her rectum contained many polypi. On September 14, 1954, diathermy treatment of multiple rectal polypi was carried out. On September 21, 1954, total colectomy and ileo-rectal anastomosis were performed. On October 12, 1954, she was discharged to her home. On May 5, 1955, diathermy treatment was applied to two recal polypi, each about one-eighth of an inch in diameter. She had had no sign of polypi since then.

The pathologist submitted the following report:

> The specimen consisted of the colon measuring about 60·0 cm. in length. The caecum and appendix together with 1·5 cm. of the terminal ileum were included in the specimen. Throughout the length of the specimen commencing in the caecum there were scattered numerous polyps ranging in size from that of a pin's head to the largest tumour which measured about 1·5 cm. in diameter. No enlarged lymph nodes were found.
>
> Microscopic examination: A section of the largest lesion confirms the diagnosis of mucosal polyposis. No malignant change can be seen in this portion of tissue.

### Anterior Resection for Diverticulitis.

Dr. Wilson's next patient, a man, aged sixty-two years, had undergone colostomy on June 6, 1955, for relief of acute intestinal obstruction of two days' duration. A mass was found in the rectosigmoid colon, but there was no other evidence of diverticulitis. On June 20, 1955, anterior resection of the rectum was performed, with end-to-end anastomosis at the pelvic floor. On July 18, 1955, closure of the colostomy opening was effected.

The pathologist submitted the following report:

> Macroscopic: An opened piece of large bowel showing an ill-defined indurated mass about its mid-length. The mass seems to be caused by a fibrous thickening of the bowel wall and attached connective tissue. An occasional small diverticulum can be traced into the indurated area.
>
> Microscopic: Sections of the mass show chronic diverticulitis. No evidence of malignancy was seen.

### Dermoid Cyst of Rectum.

Dr. Wilson then showed a single woman, aged twenty-nine years, whom he had first examined on January 19, 1954, when she complained of discomfort in the right iliac fossa. She had no other symptoms. Examination revealed a cystic mass one inch in diameter between the rectum and coccyx. On July 19, 1955, excision of the cyst was performed through the rectal wall.

The pathologist submitted the following report:

> The specimen consisted of a piece of membrane 6·5 cm. long expanded at one end to 2·5 cm. in diameter. Beneath this expanded end there was a layer of muscle 1 cm. thick.
>
> Microscopic examination: The cyst has a lining of columnar ciliated epithelium which is incomplete in the sections. The wall consists of a thin layer of rather hyaline fibrous tissue with a little plain muscle in places. There are a few small groups of mucus-secreting glands near the cyst. The appearance suggests that the lesion is a developmental cyst such as might arise from neurenteric canal or postanal gut.

### Resection of Bowel for Regional Ileitis.

Dr. Wilson's last patient was a man, aged thirty-four years, who had complained of lower abdominal pains and diarrhœa of five years' duration. On November 4, 1954, he had undergone appendicectomy elsewhere and had been told that he had Crohn's disease. The pains and diarrhœa increased in severity, and occasionally he vomited. On examination on June 26, 1955, signs of partial intestinal obstruction was elicited, and a firm mass was palpable *per rectum*. On June 27, 1955, resection of two feet of ileum was carried out, with end-to-end anastomosis. The remainder of the bowel appeared normal. Convalescence was uneventful.

The pathologist submitted the following report:

> Macroscopic: A segment of small bowel which is looped on itself to form a putty-like mass 4" in diameter. The mucosal surface shows an irregular ulceration in one area and in another a few small papillary projections.
>
> Microscopic: The piece of bowel and lymph nodes sectioned show extensive inflammatory changes, which are in keeping with a subacute Crohn's disease. The papillary projections on the bowel wall are small mucosal polyps and tags of granulomatous material.
>
> No evidence of malignancy was seen.

### Carcinoma of Colon with Obstruction.

DR. J. M. YEATES showed a woman, aged eighty-seven years, who had been admitted to hospital on October 5, 1954. She had noticed colicky pain in the lower part of her abdomen for fourteen days; and vomiting, constipation and distension for five days. She was seen on examination to be a frail old lady with much abdominal distension, but few other abnormal signs. A plain X-ray film showed gaseous distension of the proximal part of the colon. At operation, performed on the same day via a median incision, a small cicatrizing carcinoma of the pelvic part of the colon was found. Decompression was achieved by fashioning a colostomy about six inches above the growth. Three weeks later the patient's condition was so much improved as to allow the next stage of operative treatment, which consisted of resection of most of the left side of the colon including both carcinoma and colostomy site. The patient stood the procedure remarkably well and was discharged from hospital on the sixteenth day with both the median and colostomy incisions well healed. Dr. Yeates said that the manœuvre of resecting the colostomy site at the same time as the carcinoma spared the elderly patient a third operation, and several weeks of colostomy life waiting for it.

### Carcinoma of the Colon without Obstruction.

Dr. Yeates's second patient, a man, aged sixty-six years, had been admitted to hospital on June 4, 1955, complaining of diarrhœa and blood in his motions present for the last eight months. Reports from another clinic stated that a small polypus had been seen with a sigmoidoscope, but that an X-ray examination after a barium enema had shown no abnormality. Sigmoidoscopy was repeated, and revealed an obstructing lesion at 15 centimetres. After the usual preparation of the colon with sulphonamides and streptomycin, resection of most of the left side of the colon was performed on June 25, 1955. The bowels moved on the seventh day, but for the next ten days there was distressing diarrhœa, which might have been due partly to the use of streptomycin. The patient was discharged from hospital well on the nineteenth day. The pathology report stated that the lesion was a carcinomatous ulcer, five centimetres in diameter, almost encircling the lumen of the bowel. Dr. Yeates said that the negative findings at X-ray examination in the presence of such an advanced carcinoma were noteworthy. It was safe to assume that a man of sixty-six years presenting with bleeding and diarrhœa had carcinoma until it was proved otherwise.

### Pancreatic Cyst.

Dr. Yeates then showed a woman, aged thirty-one years, who had been admitted to hospital on August 31, 1954, complaining of severe pain under the lower right ribs for the past week. Four years previously a similar attack had been associated with jaundice. Examination revealed tenderness, guarding and a possible mass in the right hypochondrium. After numerous inconclusive investigations, a diagnosis of gall-bladder disease was made, but at operation a round cyst the size of a cricket ball was found above and behind the first part of the duodenum. The cyst was aspirated and yielded dark brown fluid which could have been old bile. Pathological examination detected the presence of amylase in the fluid. At that stage the patient was examined in consultation by Sir James Learmonth, who agreed with the diagnosis of pancreatic cyst and advised anastomosis to the adjacent duodenum. That was performed on September 23, 1955, and gave rise to some technical difficulty because of the thickness of the cyst wall. In subsequent discussion about the patient with Dr. Rodney Maingot, who visited the hospital soon afterwards, Dr. Maingot said that he preferred excision of the cyst as the operation of choice, but agreed that the unusual situation of the particular cyst in question, so close to the common bile duct, excluded it from such an ideal.

### Strangulated Femoral Hernia.

Next Dr. Yeates showed a woman, aged sixty-six years, who had been operated on in March, 1955, for strangulated femoral hernia, the inguinal approach being used. When the femoral canal was opened from above, the hernia could be seen but not reduced. The inguinal ligament was therefore divided, a short stump being left on the pubic tubercle. That permitted easy reduction of the hernia, which was found to contain a few inches of gangrenous small bowel requiring resection. The hernial orifice was then closed by suturing the conjoint tendon to the ligament of Astley Cooper, with interrupted silk sutures, all sutures being placed before any were tied. The inguinal ligament was then repaired with the Bunnell type of tendon suture. Dr. Yeates commented that division of the inguinal ligament rendered an otherwise difficult operation much easier in certain cases. With adequate suture there was no residual weakness, as could be verified in the patient presented.

### Stricture of the Common Bile Duct.

Dr. Yeates showed a woman, aged sixty-nine years, who had been admitted to hospital on October 21, 1954, complaining of attacks of pain in the right upper part of the abdomen present for some ten years. Although there had been no definite jaundice, the urine had often looked dark during attacks. She was an obese woman, with tenderness under the right costal margin. A cholecystogram showed a poorly filling gall-bladder. At operation the gall-bladder was found to be a mere shell of fibrous tissue, stuck onto the surface of the liver. Three stones and some biliary mud were removed from the common duct. Even small dilators refused to enter the duodenum, which was thereupon opened. Under direct vision the terminal inch of the common duct still resisted the passage of dilators, and there was evidence of chronic pancreatitis. The incision in the common duct was therefore anastomosed to the first part of the duodenum. Some bile escaped via the drainage tube for eight days, but the patient was fit for discharge from hospital on the twelfth day. She had since been free from symptoms.

### Intractable Sialectasis of the Parotid Gland.

Dr. Yeates's next patient, a woman, aged thirty-three years, had been admitted to hospital on June 17, 1955, suffering from recurrent attacks of pain and swelling in the left parotid region for ten years. Quite recently there had also been involuntary twitching of the muscles of the left side of the face. The patient had been thoroughly investigated in 1954 at another teaching hospital. Many forms of treatment, including massage, duct-dilatation, instillation of antibiotics and radiotherapy had been tried. Most of them had aggravated the condition; so that her nerves had become affected, and at times she appeared somewhat hysterical. For that reason she was extremely difficult to assess. A sialogram showed the presence of definite duct dilatation, but no calculi were visible. The patient was clamant for some decisive treatment, and was well prepared to accept the risk of facial nerve paresis, having had that possibility explained to her by all her doctors in the previous ten years. Operation was performed on June 27, 1955, induced arterial hypotension being used. The external carotid artery was first ligated. An incision was then made immediately in front of the ear, extending downwards and curving out of sight behind the angle of the mandible. A flap of skin and fat was then lifted well forwards, so as to expose the entire surface of the parotid gland. The space between the sterno-mastoid muscle and the gland was then defined, and deep in the gap the posterior belly of the digastric was found. Its nerve supply on the anterior border was then used as an easy guide to the main trunk of the facial nerve. From that point the gland was stripped off the nerve and all its branches as they appeared, Kilner's scissors being used for the dissection. Bleeding was not a problem, nor was the gland as indurated as had been feared. The patient was able to close her left eye, and raise a somewhat drooping smile a few hours after the operation. The slight facial nerve paresis disappeared after a few weeks, and at the time of the meeting complete function was present. The pathological report stated that the gland weighed 17 grammes, and that there was chronic inflammation and dilatation of many of the ducts.

### Paget's Disease of the Nipple.

Dr. Yeates then showed a woman, aged fifty-nine years, who had noticed redness and scaling on and around the left nipple for eighteen months. There was also a slight discharge from the nipple. A biopsy had been performed elsewhere twelve months previously, but no abnormality had been found. On examination of the patient on March 4, 1955, the nipple was red and scaly, with some induration. The lesion extended slightly onto the skin beyond the areola. A small surgical scar was visible. There was one large firm node palpable in the left axilla. At operation on March 7 the node was excised and examined microscopically after a frozen section had been cut. Secondary carcinoma was found. The operation was then completed as a radical mastectomy. Paraffin sections confirmed the presence of Paget's disease, with intraduct and infiltrating scirrhous carcinoma of the breast. One other involved node was also found.

### Post-Traumatic Trismus.

Another patient shown by Dr. Yeates was a woman, aged thirty-nine years, who had complained of pain and stiffness of the left side of her jaw ever since she had been rescued from drowning one year previously. The symptoms had gradually increased, and she was able to open her mouth only a very short distance, and was forced to subsist on a liquid diet. Examination confirmed the symptoms, and revealed the presence of tenderness and crepitus over the left temporo-mandibular joint. An X-ray examination showed that the joint was severely affected by osteoarthritis. On March 21, 1955, the condyle of the mandible was excised through a small incision in front of the ear, the dissection being carried out with due regard to the upper branches of the facial nerve. On the following day there was evident drooping of most of the facial muscles on the left side. That soon disappeared, but the skin over the forehead remained without a wrinkle for several months. In the meantime movement of the jaw had returned, even as early as the fourth day. At the time of the meeting movement and function were normal.

### Empyema After Appendicectomy.

Dr. Yeates finally showed a girl, aged twelve years, who had first came under his care on the twenty-seventh day after an interval appendicectomy had been performed for chronic appendicitis. The history stated that she had not made the expected recovery after operation, and had run a mysterious temperature of over 100° F. from the second day. On the eighth day a hæmatoma was diagnosed, but drainage was not instituted until the fourteenth day when much dark pus and fæcal material were evacuated. That was followed by development of a fæcal fistula. The infection next spread in an intermuscular plane under the right costal margin, where an abscess was drained through a counter-incision on the thirtieth day. A few days later abnormal signs developed in the right side of the chest, and on the thirty-seventh day six ounces of fæcal-smelling pus were aspirated. An X-ray examination at that stage showed all the signs characteristic of a right subphrenic abscess, and the child's condition was critical. With local anæsthesia, the right twelfth rib was swung back on its bed, the diaphragm incised and the subphrenic space thoroughly explored. Surprisingly, no abscess was found. The rib was replaced and the wound closed. Treatment was then concentrated on the empyema, which was aspirated daily, and the pleural cavity was irrigated with streptomycin in saline, culture having shown the presence of a paracolon bacillus sensitive to the antibiotic. Steady improvement followed for the first

time since operation, and by the fifty-second day the pleura was dry. Meanwhile the fæcal fistula had closed, and the several abdominal incisions were beginning to heal. Dr. Yeates said that it need hardly be added that from the first sign of infection the child had received a vast array of antibiotics. He went on the comment that there was little doubt that bleeding from the mesoappendix was the prime cause of such a formidable series of complications. Silk ligatures were less likely to slip than catgut; and the mesoappendix should always be critically inspected just before the abdomen was closed.

### Prognathism.

DR. E. M. CORTIS showed a patient who had had asymmetrical prognathism treated by Kostecka's operation. The patient, aged twenty-seven years, had noticed that for a year his jaw had been progressively growing forwards and to the right, so that there were only two teeth which he could make meet. He had developed severe indigestion. X-ray examination showed enlargement of the entire left half of the mandible. Professor Arnott and Mr. Corbett, of the Sydney Dental Hospital, first cemented upper and lower cast-metal ferrule splints to the teeth. At Sydney Hospital bilateral osteotomies of the ascending rami of the mandible above the inferior dental foramina were performed by Kostecka's technique. A large hollow needle was inserted through the buccal mucosa at the level of the third upper molar tooth, and its tip was insinuated above the sphenomandibular ligament and made to hug the bone until it was brought out through a tiny stab incision behind the mandible. By that means a Gigli saw was introduced, and this was used to divide the ascending ramus in a downward as well as outward direction. The procedure was repeated on the other side, the jaw was pushed back so that the teeth were in accurate occlusion, and the upper and lower splints were wired together. On removal of the splints after six weeks, clinical union was firm, and the occlusion of the teeth was vastly improved.

### Depressed Malar Fracture.

Dr. Cortis then showed a patient who had had an old depressed malar fracture treated by the implantation of acrylic. Twenty years previously the patient had been involved in a car smash, his head being crushed between the side of the vehicle and the ground. He complained of diplopia on looking sideways. X-ray examination showed an old depressed fracture of the malar bone, with marked widening of the fronto-malar suture and gross depression of the lateral half of the orbital floor. A small incision was made in the malar region, and over the whole of the depressed area the bone was freed from the overlying soft tissues. Also the periosteum was elevated over the lateral half of the orbital floor. Acrylic powder was inserted by means of the "acrylic gun", so as to mask the deformity and elevate the periosteum of the floor of the orbit.

### Congenital Nasal Deformity.

Dr. Cortis then showed a patient who had had a congenital nasal deformity treated by reconstruction with a bone graft from the iliac crest. Dr. Bear had performed a preliminary submucous resection of the septum.

### Alwall's Artificial Kidney Unit.

Pending the arrival of other units of the Alwall artificial kidney or external dialyser, for use in the recently established renal unit at Sydney Hospital, part of the equipment was shown in the department of urology.

DR. KEITH KIRKLAND explained that the Alwall unit provided only one therapeutic approach in a renal unit or laboratory. He pointed out that a full understanding of electrolyte and fluid balance enabled corrections to be made by other more conservative means in many cases. The majority of patients could be adequately treated by intravenous therapy, exchange transfusions, the use of ion exchange resins and internal dialysis, such as peritoneal lavage. A combination of any of those measures would often obviate the need for external dialysis.

The principle used in the Alwall kidney was that of passing heparinized blood, generally from the radial artery of a patient, through about twenty metres of "Cellophane" tubing, bathed in a suitable electrolyte solution. The purified blood was returned conveniently to a vein in the antecubital area. The "Cellophane" was wound round a perforated cylinder, which was itself encased in another cylinder, the space between the two being such as to allow only a thin layer of blood to occupy the tubing. The process was continued for anything up to eight hours, and during that time the electrolyte solution was replaced from an adjacent container. Circulation of the solution was maintained by a rotator in the bath space.

DR. IAN POTTS, in discussing the indications for the use of the external dialyser, pointed out that it had its greatest use in the management of acute renal failure or so-called "kidney shut down". When the failure was acute with no background of chronic renal damage, total recovery could occur. In addition a great deal of temporary benefit could be conferred on patients with chronic renal disease when the condition was not too advanced.

### Urological Cases.

DR. H. H. PEARSON and DR. J. E. BLACKMAN presented a series of patients with urological conditions.

A boy, aged eighteen years, had been admitted to hospital with complete *ectopia vesicæ*. Although living in the country, he was not a happy member of society with such a lesion. His right kidney was functioning normally, but the left kidney had been non-functioning since the age of five years. (Coloured plates were shown of the ectopic bladder, complete with epispadias.) At operation the bladder was excised after preliminary transplantation of the right ureter into the rectum. The abdominal deficiency was closed with a "Z" plastic procedure. The patient's abdominal scar was now healed except for a small defect above the penis, which was to be later covered by a split skin graft.

A man, aged sixty-eight years, had presented with a history of hæmaturia on and off for five weeks, and on cystoscopy was found to have a large tumour involving the vault of the bladder. It was an extrinsic carcinoma from the sigmoid colon, invading the bladder. At laparotomy Dr. Pearson resected the colon and most of the bladder, leaving only the bladder neck and trigone. The bladder was then reconstituted by using the distal rectal stump as an artificial extension and that was sutured to the remaining part of the bladder neck. The patient made a good recovery and now passed urine satisfactorily *per urethram*, although he still passed a little mucus *per rectum*. He had a terminal left iliac colostomy.

Dr. Blackman showed the cystograms taken before operation, demonstrating the filling defect of the carcinoma in the vault, and after operation, showing the capacity and shape of the rectal bladder.

A man, aged fifty-one years, had early in 1954 undergone total prostatectomy for early carcinoma performed by Dr. Pearson. His progress had been very satisfactory until January, 1955, when he complained of pain in the right hip. At that time nothing abnormal was found on rectal examination or on X-ray examination of the pelvis and spine, and the serum acid phosphatase content was 4·4 King-Armstrong units. On May 5, 1955, pain recurred and was more severe; and although the X-ray findings were negative, administration of stilbœstrol was commenced in an effort to relieve the pain. On June 30 an X-ray examination showed numerous areas of sclerosis typical of secondary prostatic carcinoma and the serum acid phosphatase level had risen to five King-Armstrong units. In spite of the exhibition of stilbœstrol, the pain continued and became more severe and was not lessened by orchidectomy. At that stage bilateral adrenalectomy was planned, in view of his intense misery. It was performed on August 10, 1955, through the bed of the twelfth rib on each side. There was immediate and marked relief of pain, and the patient made an uninterrupted recovery. At the meeting the patient was shown, fit and well. He was maintained on treatment with orally administered cortisone, 25 milligrammes in the morning and 12·5 milligrammes at night. The sections of the primary prostatic carcinoma and the X-ray films showing the progress of the disease were shown.

### Radiology Demonstration.

From the radiology department a series of chest X-ray films of healthy young adult males (resident medical officers) was shown. Films had been exposed at full inspiration and at full expiration. Visitors were invited to comment on the films and, on asking, were informed of the apparent good health of the subjects and of the variation in technique between the two types of picture.

The following observations were made: (i) that most people were prepared to comment on the films without asking for details of the clinical condition of the patient; (ii) that when it was mentioned that the subjects were healthy young adults, there was a tendency to insist that, notwithstanding that fact, the films taken in expiration were abnormal.

Other films were on display demonstrating a variety of pathological conditions.

### Unusual Tumour of the Liver.

DR. A. A. PALMER showed specimens and photomicrographs of the liver of a Chinese male subject, aged sixty-seven years. There was a history of congestive cardiac failure and hypertension, and death was due to cerebral hæmorrhage. There were no symptoms of liver disease. The liver, however, was everywhere abnormal, with yellow, brown and red mottling, and there were several hæmorrhagic nodules. The sections showed widespread angiomatous dilatation of the sinusoids with proliferation of parts of the vascular endothelium. The hæmorrhagic nodules consisted of malignant newgrowth, which appeared to be arising from the vascular endothelium, and hence was regarded as a malignant hæmangioendothelioma. No vascular abnormalities or tumours were found in other organs.

### Radioactive Chromium Technique for Determining Red Blood Cell Life Span.

DR. G. A. W. JOHNSTON and MR. J. DAVIS demonstrated the radioactive chromium technique for determining red blood cell life span *in vivo* and red blood cell volume. It was explained that, briefly, the principle of the method depended upon the fact that chromium was a constituent of the normal red blood cell. Red blood cells were incubated in the presence of the radioactive isotope of chromium, $Cr^{51}$, which was taken up and became firmly bound. For practical purposes complete loss of chromium corresponded with red cell disintegration or death. It had been found that radioactive chromium, once liberated, was not reutilized by other cells. The patient's or donor's cells were tagged and injected intravenously. When mixing in the circulation was complete, after ten or twenty minutes, a sample was collected. Subsequent samples were collected as required, and the radioactivity of each was determined by a scintillation counter. The radioactivity of the first sample was taken as 100%. Radioactivity in subsequent samples, after application of correction factors, was expressed as a percentage of the initial sample. Graphs were shown illustrating how results were plotted. The red cell life span was the time taken for complete disappearance of radioactive chromium from the blood.

It was pointed out that the technique might be used for estimating the red blood cell and blood volume. The volume of tagged red cells injected was measured accurately. The total amount of radioactivity in the volume of cells injected, divided by the amount in the same unit volume of the ten to twenty minute sample of blood, gave the dilution, from which the blood volume could be calculated.

### Electromyography.

MR. J. DAVIS demonstrated the apparatus for electromyography. The apparatus, consisting basically of a preamplifier, twin-beam oscillograph and tape recorder, was arranged so that it could be inspected while it was in use. A volunteer subject had electrodes applied over the *flexor sublimis digitorum*, and the electrodes were connected to the apparatus. Members were invited to ask the subject to flex a finger and viewed the resulting electromyogram on the screen of the oscillograph. The activity was also simultaneously recorded by the tape recorder and subsequently "played back" through the oscillograph. Examples of the film trace taken from the oscillograph were also displayed.

### Electroencephalography.

DR. C. B. HUDSON and MR. J. DAVIS displayed a number of abnormal electroencephalographic records. Each was selected as being a classical example of its particular type. Each record had attached to it a brief history of the patient, the electrocardiographic report, and in some cases a summary of operative findings.

### Physiotherapy Demonstration.

A demonstration with an accompanying explanation was given by the physiotherapy department of the type of physical therapy used in treating emphysematous and asthmatic patients. One patient with emphysema, aged fifty-two years, and two asthmatic patients, aged respectively twelve and twenty-nine years, demonstrated the exercises. Their case histories were presented indicating improvement in the use of the diaphragm and lower costal areas and in relaxation of the upper part of the chest. The emphysematous patient had increased his exercise tolerance, and the asthmatic patients had gained some physical control of their attacks.

### Necrobiosis Lipoidica Diabeticorum.

DR. EWAN MURRAY-WILL showed a married woman, aged thirty-four years, who gave the history that at the age of twelve years both shins had been scalded with boiling water. Two years before the time of the meeting the scars had been knocked with a crate and had become bruised and tender. Reddish, scaly plaques had developed which were slowly spreading. The lesions presented the appearance of *necrobiosis lipoidica diabeticorum*.

A glucose tolerance test produced findings typical of severe *diabetes mellitus*. A biopsy had been performed, but the report was not yet to hand.

Dr. Murray-Will said that the condition was a peculiar degeneration of the connective tissue of the skin which occurred principally on the lower extremities, mainly in women, and was characterized at first by oval, firm, reddish patches with yellowish centres which developed later into scleroderma-like plaques. It might also be found sparsely on the upper extremities, trunk and face. It might occur at any age, and trauma might play a part in its development. A high percentage of the lesions occurred in patients suffering from *diabetes mellitus*, but they might also be found in non-diabetic subjects.

### Lichen Sclerosus et Atrophicus.

Dr. Murray-Will also showed a married woman, aged fifty-seven years, suffering from *lichen sclerosus et atrophicus* of fourteen years' duration. The lesions had first developed on the front of the chest and later appeared in the axillæ, in the upper end of the gluteal cleft and on the nape of the neck.

Dr. Murray-Will explained that the condition was a slowly developing, chronic, localized eruption of unknown ætiology. It was an atrophic condition of the skin characterized by ivory white, firm macules and papules of polygonal and irregular shape, which might be discrete or grouped into plaque formation. Keratotic follicular plugs were distinctive features, but they might be absent when ointment had been used. Itching was slight or absent. The neck, shoulders, axillæ, forearms, vulva and perineum were commonly affected. For treatment the patient was having chloroquin diphosphate 250 milligrammes daily.

### Lindau-von Hippel's Disease.

DR. B. G. HILL showed a patient suffering from Lindau-von Hippel's disease. He said that the condition was a systemic angioblastic disorder of the central nervous system, often associated with a cystic pancreas or cystic kidneys and more rarely with hypernephroma, cystic tumours of the epididymus, and angiomatosis of the liver, and occasionally with capillary nævi of the skin. Only a minority of patients, however, displayed the complete range of intracranial and visceral lesions associated with ocular signs.

The lesion was either solid or cystic, and hæmangioblasts were the characteristic cells, capable of forming solid cords as well as reticulations and adventitious vessels.

Both eyes were affected in one-third of the cases, multiple tumours were often present, and a familial incidence was common. Characteristic of the ocular condition were (i) fullness of the retinal veins in one segment, (ii) angiomatous formation of the retina, usually far out in the periphery on the temporal side, (iii) massive retinal exudate, and (iv) partial retinal detachment, eventually becoming complete. The changes in the retina were thus progressive; following complete retinal detachment uveitis and complicated cataract developed, leading eventually to *phthisis bulbi*.

Treatment was designed to obliterate the angiomatous mass by irradiation, application of surface or penetrating diathermy to the overlying sclera, or penetration of the tumour with an electrolysis needle. Results were not generally satisfactory, frequent complications of surgical interference being hæmorrhage and *retinitis proliferans*. Probably the application of radon seeds offered the best chance of success.

The patient presented had the ocular manifestations with a history and one sign indicating central nervous system involvement. She was a girl, aged thirteen years, who had presented with a history of "peculiar turns"—shaking and abnormal movements of the arms for a few moments (sometimes both arms, sometimes one, more often the right), with momentary "loss of memory" during the fit. On the previous day, when sitting down, she had had a "fit", commencing in the left hand and spreading up the arm, with loss of consciousness. She had no memory of any struggling and no incontinence. For the past two months she had noticed

poor vision in the right eye, but no headache, vomiting or diplopia. Her mother stated that about eighteen months previously the patient had fallen from a bicycle, hitting her forehead, but had not lost consciousness and suffered no subsequent headache. About six months later she had a fit in which the arms and legs first went rigid; then she lost consciousness, and her limbs "worked". Minor fits followed until the recent major fit already described. Investigation of the family history revealed no ocular disorder, nævi, abdominal tumours or epilepsy.

On examination the patient was found to have slight facial asymmetry. The visual acuity was 6/36 in the right eye and 6/6 in the left. She was emmetropic in both eyes. The pupils were equal and reacted normally. The muscles were normal in balance and action. Examination of the right fundus showed early papillœdema and solid exudates at the posterior pole. Angiomatosis was noted at the lower temporal periphery of the retina. The lower temporal veins were full, but not unduly tortuous. The left fundus was normal. Field defects corresponded to a right retinal lesion and did not indicate involvement of the visual tract.

One week later, on her admission to hospital, the patient was normal on general physical examination. Plain X-ray examinations showed no cranial, intracranial or chest lesions. On carotid arteriography examination of the wet film showed in the antero-posterior and lateral views nothing abnormal, but in the right oblique view a possible aneurysm of a cerebral vessel.

The erythrocyte sedimentation rate was 18 millimetres per hour. The results of Wassermann and Kahn tests were negative. The findings on full blood count were normal. The Mantoux reaction was positive.

On October 27, 1954, the electroencephalogram was abnormal and suggested a deep left temporal lesion.

On December 16, 1954, when in a convalescent home, the patient had another "turn" at 8 a.m., with numbness of both hands, then shaking of the hands, and finally loss of consciousness. She recovered rapidly, but a frontal headache remained. On examination of the patient the papillœdema had increased in the right eye, and solid exudates were now extensive. Early papillœdema was present in the left eye.

On January 24, 1955, a small retinal detachment had developed in the right eye, in the lower quadrant. Papillœdema was less on the left side.

On March 1, 1955, she stated that she had had two attacks of dizziness one month previously, on successive days. The visual acuity was 6/9 in the right eye and 6/6 in the left. Retinal detachment on the right side had increased, however, and a considerable amount of solid intraretinal exudate was present, the vessels in the area remaining full. The right-sided papillœdema was less, and the left fundus was now normal.

On May 31, 1955, no further general symptoms had been experienced. The visual acuity was 6/12 in the right eye and 6/6 in the left. No change had occurred in the fundi.

At the time of the meeting the visual acuity was 6/9 (partly) in the right eye and 6/6 in the left. Minor fits continued several times a week.

### The Girdlestone Operation for Fractured Femur.

DR. R. HODGKINSON showed two patients to demonstrate "Girdlestone" excision of the head and neck of the femur.

A woman, aged eighty-one years, had been admitted to Sydney Hospital on October 4, 1954, suffering from an intracapsular fracture of the neck of the right femur. A Smith-Petersen pin was inserted on October 11, 1954, but because of the poor nutrition it cut out and was removed on April 21, 1955. Efforts were made to get the patient to walk without further surgical intervention, but finally she was unable even to sit because of the severe pain. On May 21, 1955, the head and neck of the right femur were excised. Skin traction was applied for three weeks. The wound was well healed, and then early weight-bearing was commenced. Despite five-eighths of an inch shortening the patient was free of pain while sitting and was able to walk 100 yards or more.

A woman, aged seventy-six years, had been admitted to hospital with a fractured neck of the femur on March 11, 1954. A Smith-Petersen pin was inserted on March 17, 1954. The pin began to be extruded, and she was treated by traction for some months. On January 10, 1955, the head and neck of the right femur were excised. She was treated by traction for three weeks and then commenced walking, the leg being protected by means of crutches. She was now walking with three-quarters of an inch shortening, but no pain or discomfort, with the help of one crutch.

### Spondylolisthesis.

Dr. Hodgkinson also showed three patients with spondylolisthesis, who had been treated by excision of the spinous process, lamina, interarticular facet and lower part of the *pars interarticularis* of the vertebræ.

A man had suffered a back injury on September 14, 1954, with resulting pain in the groin extending into both buttocks. No neurological signs were found suggesting nerve root irritation. On December 7, 1954, a decompression operation was performed. On June 8, 1955, he resumed work of a light nature. He was out of bed after operation in two weeks, as he had severe chronic bronchitis.

A man had been crushed by a tractor on August 6, 1954. He developed back pain with some radiation into the right hip and knee. No definite abnormal neurological signs were found. At operation on July 6, 1955, decompression was carried out. He still had some persistent pain in the buttock.

A man had injured his back lifting timber on March 15, 1955. The back pain persisted despite conservative treatment. No neurological signs were found suggesting nerve root irritation. On July 28, 1955, a decompression operation and spinal fusion with an "H" graft were carried out. At the present time he was still in a jacket.

### Volkmann's Contracture.

A girl, aged seven years, had suffered a fracture of the middle and lower thirds of the right radius and ulnar with complete overlap. On December 27, 1954, the fractures were reduced under "screening". The fractures were unstable with interference with circulation. They were remanipulated. On January 13, 1955, she was transferred to Sydney Hospital. At that stage there was gross swelling. Some collateral circulation was present, but no sensation was apparent in the hand. Blisters were present over the forearm with full-thickness slough in areas. Split-thickness grafts were applied, the bones sequestrated, and the muscles finally contracted. It was a typical Volkmann contracture.

### Stent Graft for Chronic Osteoarthritis.

A woman, aged thirty-three years, had had chronic osteoarthritis of the left tibia and discharging sinuses for two and a half years. On June 13, 1952, after curettage, the cavity was filled with bone chips and covered with a rotation flap. That failed, and the cavity continued to discharge chips. On February 22, 1955, after curettage, the cavity was left open. It was packed with antibiotics till granulation was present, and then split thickness skin was applied over dental stent to fill the cavity with epithelium.

### Pre-Slip Femoral Epiphysis.

Dr. Hodgkinson displayed X-ray films to show the slight change discerned in the epiphysis and metaphysis when the head of the femur was ready to slip. Clinically the condition had been associated with some pain and limitation of movement. A special sharpened Smith-Petersen pin had been inserted to hold. The patient was now walking on a pylon-type weight-relieving caliper.

### Almoner's Department.

The almoner's department presented a project on "Social Problems Associated with the Care of Cancer Patients". A series of seven illustrated posters, together with an explanatory leaflet, was prepared giving details of common social problems which arise for patients receiving treatment for cancer. It was explained that a survey had been carried out of 532 patients with malignant disease referred to the almoner's department for assistance by medical officers over a period of six months from January 1 to June 30, 1955.

That had shown that social difficulties with which patients had to contend were many and varied, but, in general, centred about the need for special hospital or nursing care, financial assistance, adequate transport facilities and continued supportive help both for themselves and for their families. It was emphasized that all the patients were referred at different stages of their illness, and thus it was possible to review only their immediate needs or, at most, their changing needs for a period up to six months.

*Supportive Help to Patients and Their Relations.*—A total of 461 patients (87%) and their relations were given supportive help. The very nature of the disease, its treatment, particularly prolonged courses of radiotherapy, and the subsequent follow-up, all created special social difficulties. To assist patients to cooperate fully in medical treatment it was often necessary to investigate and interpret the social situa-

tion in terms of the medical requirements and to maintain contact over a prolonged period.

*Special Hospital Care.*—Of the patients under review 10% required care in a special hospital. Of the 51 patients admitted to special hospitals, 13 went to Moorong, Ryde; 16 to the Home of Peace for the Dying, Petersham; six to the Sacred Heart Hospice, Darlinghurst; nine to the Cancer Ward, Liverpool Hospital; and seven to district hospitals.

*Nursing Care.*—About 8% of patients needed nursing care. Care in various private nursing homes was arranged for 21 patients, whilst domiciliary care was provided for 24 patients with the assistance of the Sydney District Nursing Association, Our Lady's Brown Nurses and private nurses.

*Convalescence.*—About 3% of patients required convalescence, either post-operatively or after radiotherapy, in a special convalescent home. Convalescence was arranged for 18 patients: eight at Strickland Convalescent Hospital, Vaucluse; three at the Thomas Walker Convalescent Hospital, Concord; four at Carrington Convalescent Hospital, Camden; three elsewhere, including the War Veterans' Home, Narrabeen.

*Supervised Care during Radiotherapy.*—Some 11% of patients were in need of supervised care during their course of radiotherapy. That group of patients came from the country, from outer suburban areas with inadequate transport facilities, from districts so far removed from the treatment centre that daily travel would prove too fatiguing and from homes where the living conditions were unsuitable. Of the 59 patients in this category, 46 went to Strickland Convalescent Hospital, Vaucluse, and the remaining 13 were either cared for in private nursing homes or accommodated in special homes or hostels.

*Financial Assistance.*—A total of 24% of patients were in financial difficulties. Altogether 129 patients were helped financially: 71 were given advice about statutory benefits, mainly in connexion with claims for sickness benefit or an invalid pension through the Commonwealth Department of Social Services; 23 were either referred direct to the State Department of Labour and Industry and Social Welfare for immediate assistance pending the granting of Commonwealth benefits or for supplementary allowances to meet the costs of special diets, or were given emergency help for food and accommodation from the almoner's department's funds; 35 were assisted with the cost of fares to and from the hospital for treatment, either in a grant from the almoner's department or in the form of travel passes from the Department of Labour and Industry and Social Welfare.

*Transport.*—About 29% of patients lacked proper transport facilities. Of the 154 patients assisted in this way, 75 were transported in the Sydney Hospital ambulance, 51 in district ambulances, 19 in hire cars or taxis, and nine in cars belonging to voluntary agencies, including members of the Rotary Club of Sydney, the Australian Red Cross Society Transport Service and Voluntary Aid Detachments.

## Out of the Past.

***In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.***

### A GRATEFUL PATIENT.[1]

[ALTHOUGH D'Arcy Wentworth became Principal Surgeon in the settlement at Sydney Cove he had no medical degree and the extent of his medical knowledge is doubtful. However, one at least of his patients who became printer and publisher of the first newspaper in the settlement (the *Sydney Gazette*) was full of appreciation of his skill and kindness and wrote to him under date 21st November, 1801.]

Sir,

I should before your departure from Sydney have troubled you with a Letter of Thanks for the great Care and Attention you were pleased to shew during my painful and dangerous Malady, but was prevented from so doing from an Idea that until the wounds in my foot were healed such a step might have been considered by you as premature. As my Delay in this most necessary Duty proceeded neither from unbecoming Neglect or a want of Knowledge in its Propriety permit me now to inform you sir that my Cure is at length perfected and that to your exalted Skill and unceasing Attention I render my most grateful Acknowledgments and sincere Thanks. I shall always esteem you Sir as the Preserver of my Life and as the immediate Instrument of Omnipotency in restoring me to the use of my Limbs without which from my unfortunate Situation in the Colony Life must ever have remained a heavy Burthen.

Hoping that you will in your distinguished Goodness condescend to accept the humble Tribute of my Thanks. I know no gratification equal to that of acknowledging myself,

Sir,

Your grateful and respectful Servant,

GEORGE HOWE.

[1] From the original in the Mitchell Library, Sydney.

## Post-Graduate Work.

### THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

SPECIAL COURSES FOR GENERAL PRACTITIONERS.

THE Post-Graduate Committee in Medicine in the University of Sydney announces the following programmes of special courses for general practitioners, to be held during August, 1956.

#### Week-End Course in Pædiatrics.

The following week-end course in pædiatrics will be held in the Lecture Theatre, Royal Alexandra Hospital for Children, on Saturday and Sunday, August 4 and 5, under the supervision of Dr. D. G. Hamilton:

Saturday, August 4: 9.15 a.m., "Allergic Problems of Infancy and Childhood and Their Treatment", Dr. S. E. L. Stening; 10.30 a.m., "Vomiting in the First Month of Life", Dr. E. S. Stuckey; 11.30 a.m., "Pædiatric Emergencies", Dr. John Quoyle; 1.45 p.m., demonstration of cases, Dr. D. G. Hamilton; 2.45 p.m., "Problems of Infant Feeding", Dr. Kathleen Winning; 4 p.m., "The Epidemiology, Prevention and Diagnosis of Acute Anterior Poliomyelitis", Dr. R. H. Vines.

Sunday, August 5: 9.15 a.m., "Some Hæmatological Problems of Childhood and Their Management", Dr. S. E. J. Robertson and Dr. D. Kerr Grant; 10.30 a.m., "Therapeutic Problems", Dr. J. M. Alexander; 11.30 a.m., "Treatment of Herniæ in Childhood", Dr. J. Steigrad; 2 p.m., "What Does This Murmur Mean?", Dr. D. S. Stuckey; 3 p.m., "Burns", Dr. D. L. Dey; 4 p.m., question time, Dr. Malcolm Edwards and Dr. D. L. Dey.

The fee for attendance, including luncheons, is £4 14s., and the closing date for applications is July 25, 1956. The fee for members who do not require luncheons is £4 4s.

#### Course in Obstetrics and Gynæcology.

A course in obstetrics and gynæcology by the staff of the Women's Hospital, Crown Street, Sydney, will be held at the hospital for two weeks from August 13 to 24, under the supervision of Dr. W. G. McBride. Enrolments are limited to 14 post-graduate students in residence and 12 attending as external students. The programme is as follows:

Monday, August 13: 9.30 a.m., welcome and tour of the hospital; 11 a.m., "Functional Uterine Bleeding", Dr. Alan Grant; 2 p.m., operative demonstration; 4 p.m., case presentation.

Tuesday, August 14: 9.30 a.m., "Early Diagnosis of Uterine Cancer", Dr. J. Chesterman and Dr. J. Murray Moyes; 11 a.m., "Modern Trends in the Treatment of Uterine Cancer", Dr. J. Chesterman and Dr. L. Atkinson; 2 p.m., demonstration of methods of Sims test, Rubin test and salpingography in the investigation of sterility, Dr. Alan Grant and Dr. R. Mackey.

Wednesday, August 15: 9.30 a.m., "Pelvic Pains with Negative Findings", Dr. Alan Grant; 11 a.m., Cancer Clinic—demonstration of cases; 2 p.m., operative demonstration; 4 p.m., case presentation.

Thursday, August 16: 9.30 a.m., "Stress Incontinence and Prolapse", Dr. R. B. C. Stevenson; 11 a.m., "Endometriosis", Dr. S. Devenish Meares.

Friday, August 17: 9.30 a.m., "The Retroverted Uterus", Dr. F. A. Bellingham; 11 a.m., demonstration of common pathological tests, Dr. B. Arnold; 3 p.m., question session.

Monday, August 20: 9.30 a.m., surgical pædiatrics; demonstration of cases by Dr. E. Stuckey; 11 a.m., "Post-Maturity", Dr. Malcolm Drummond; 2 p.m., ward round; 3.30 p.m., "Expectant Treatment of Placenta Prævia", Dr. D. McGrath.

Tuesday, August 21: 9.30 a.m., "Care of the Premature Infant", Dr. S. E. L. Stening; 11 a.m., "Feeding Problems", Dr. C. W. G. Lee; 2 p.m., ward round; 3.30 p.m., "Uterine Fibroids Complicating Pregnancy", Dr. R. Mackey.

Wednesday, August 22: 9.30 a.m., "The Role of Cæsarean Section in Present-Day Obstetrics", Dr. K. A. McGarrity; 11 a.m., "Problems Associated with Abortions", Dr. W. G. McBride; 2 p.m., operative demonstration—Cæsarean section; 3.30 p.m., "Anæsthesia for Cæsarean Section", Dr. C. N. Paton.

Thursday, August 23: 9.30 a.m., symposium on "Medical Conditions Complicating Pregnancy", discussion by Dr. Richmond Jeremy, Dr. F. H. Hales Wilson, Dr. Helen Taylor and Dr. T. Robertson; subjects for discussion—hypertension and heart disease; 2 p.m., question session.

Friday, August 24: 9.30 a.m., "Labour following Cæsarean Section", Dr. R. McD. Bowman; 11 a.m., "Breech Presentation", Dr. R. D. Macbeth.

Operative demonstrations will include technique of hysterectomy, technique of Manchester operation, methods of cure of stress incontinence of urine, treatment of ovarian tumours, and Cæsarean section. It is hoped that the operative sessions will be televised.

The fees for attendance are £17 17s. (including board and residence) or £12 12s. (external attendance). Candidates should take up residence on Sunday afternoon, August 12. Early written application is essential, as enrolments will be made in order of receipt of fees, and the list will be closed as soon as the required number of application is received.

### Week-End Course in Gastro-Intestinal Diseases.

The following week-end course in gastro-intestinal diseases will be held in the Scot Skirving Lecture Theatre, Royal Prince Alfred Hospital, on Saturday and Sunday, August 18 and 19, under the supervision of Dr. Stanley Goulston:

Saturday, August 18: Symposium, "Diseases of Œsophagus and Stomach"—chairman, Dr. Innes A. Brodziak; 9.30 a.m., "Dysphagia", Dr. George Hall; 10 a.m., "Œsophageal Stricture", Dr. Brian P. Billington; 10.30 a.m., "Gastric Ulcer", Dr. W. E. Fisher; 11 a.m., "Duodenal Ulcer", Dr. Brian P. Billington; 11.30 a.m., "Indication for Gastric Surgery", Dr. W. E. Fisher; 12 noon, "Post-Gastrectomy States", Dr. Stanley Goulston. Symposium, "Diseases of the Small and Large Bowel"—chairman, Dr. W. A. Bye; 2 p.m., "Syndromes of Functional Disorders of the Bowel", Dr. D. W. Piper; 2.30 p.m., "Steatorrhœa: Clinical Features and Management", Dr. Ralph Reader; 3 p.m., "Diarrhœa: Causes and Clinical Features", Dr. A. E. McGuinness; 3.30 p.m., "Diarrhœa: Management", Dr. A. E. McGuinness; 4.15 p.m., "Modern Outlook in Ulcerative Colitis", Dr. Bruce Hall.

Sunday, August 19: Symposium, "Diseases of Liver and Pancreas"—chairman, Dr. A. W. Morrow; 9.30 a.m., "Reaction of Liver to Injury", Dr. V. J. McGovern; 10 a.m., "Biochemical Changes in Liver Disease", Dr. David Church; 10.30 a.m., "Portal Hypertension: Development and Features", Dr. A. W. T. Edwards; 11 a.m., "Portal Hypertension: Management", Professor C. R. Bickerton Blackburn; 11.30 a.m., "Acute Pancreatitis: Management", Dr. Vernon Barling; 12 noon, "Chronic Relapsing Pancreatitis: Management", Dr. K. W. Starr.

The fee for attendance is £3 3s., and the closing date for applications is August 10, 1956.

### Course in Dermatology.

The following course in dermatology will be held for one week from Monday to Friday, August 27 to 31, under the supervision of Dr. Richard B. Perkins:

Monday, August 27: At the Royal Alexandra Hospital for Children: 9.45 a.m., demonstration of cases, out-patient department, Quay Street, Dr. R. F. A. Becke; 11 a.m., "Infantile Eczema and Napkin Dermatitis", Lecture Theatre, Main Hospital, Dr. R. F. A. Becke. At the Royal North Shore Hospital: 2 p.m., "Dermatitis and Eczema", Part I, Students' Lecture Theatre, Dr. W. Keith Myers; 3 p.m., demonstration of cases, out-patient department, Dr. W. Keith Myers; 4.30 p.m., "Dermatitis and Eczema", Part II,

### DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED JUNE 16, 1956.[1]

| Disease. | New South Wales. | Victoria. | Queensland. | South Australia. | Western Australia. | Tasmania. | Northern Territory. | Australian Capital Territory. | Australia. |
|---|---|---|---|---|---|---|---|---|---|
| Acute Rheumatism | 3(1) | 2(1) | 7(7) | 3 | .. | .. | .. | .. | 15 |
| Amœbiasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Ancylostomiasis | .. | .. | 1 | .. | .. | .. | .. | .. | 1 |
| Anthrax | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Bilharziasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Brucellosis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Cholera | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Chorea (St. Vitus) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Dengue | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Diarrhœa (Infantile) | 7(6) | 6(3) | 8(2) | .. | 8(1) | .. | .. | .. | 29 |
| Diphtheria | 3(2) | 3(3) | 2(2) | 5(5) | 3(3) | .. | .. | .. | 16 |
| Dysentery (Bacillary) | .. | 3(2) | 3(2) | .. | .. | .. | .. | .. | 6 |
| Encephalitis | .. | 1 | .. | 1(1) | .. | .. | .. | .. | 2 |
| Filariasis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Homologous Serum Jaundice | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Hydatid | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Infective Hepatitis | 48(22) | 76(19) | .. | 7(3) | 5(2) | 8 | .. | 3 | 147 |
| Lead Poisoning | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Leprosy | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Leptospirosis | .. | .. | 8 | .. | .. | .. | .. | .. | 8 |
| Malaria | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Meningococcal Infection | 1 | 2(1) | 1 | .. | 1 | .. | .. | 1 | 6 |
| Ophthalmia | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Ornithosis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Paratyphoid | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Plague | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Poliomyelitis | 7(1) | 11(3) | 2(2) | .. | 3(1) | .. | .. | .. | 23 |
| Puerperal Fever | 1 | .. | .. | .. | .. | 1 | .. | .. | 2 |
| Rubella | .. | 3(2) | .. | 4(4) | 3 | .. | .. | .. | 10 |
| Salmonella Infection | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Scarlet Fever | 13(8) | 24(12) | 5(2) | 5(2) | .. | .. | .. | .. | 47 |
| Smallpox | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Tetanus | .. | .. | .. | .. | 1(1) | .. | 1 | .. | 2 |
| Trachoma | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Trichinosis | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Tuberculosis | 43(28) | 25(16) | 11(3) | 7(4) | 5(4) | 8(5) | .. | .. | 99 |
| Typhoid Fever | .. | .. | 1 | .. | .. | .. | .. | .. | 1 |
| Typhus (Flea-, Mite- and Tick-borne) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Typhus (Louse-borne) | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| Yellow Fever | .. | .. | .. | .. | .. | .. | .. | .. | .. |

[1] Figures in parentheses are those for the metropolitan area.

Students' Lecture Theatre, Dr. M. B. Lewis. At the Stawell Hall, 145 Macquarie Street, Sydney: 8.15 p.m., symposium on "Pyogenic Infections of the Skin, Their Prevalence and Prevention", Dr. Edgar Thomson, Dr. Wilfred H. Cary and Dr. A. Geoffrey Finley.

Tuesday, August 28: At the Royal Alexandra Hospital for Children: 10 a.m., demonstration of cases, Birth Marks Clinic, Main Hospital, Dr. Henry Sharp; 10.45 a.m., "Urticaria and Birth Marks", Lecture Theatre, Main Hospital, Dr. Henry Sharp. In the Number 2 Lecture Theatre, New Medical School: 2 p.m., "Tinea", Dr. Miles Havyatt; 3 p.m., "Lupus Erythematosus, Psoriasis, Lichen Planus, Erythema Multiforme and Erythema Nodosum", Dr. E. J. C. Molesworth. At the Royal Prince Alfred Hospital: 4.30 p.m., demonstration of cases, out-patient department, Dr. E. J. C. Molesworth.

Wednesday, August 29: At Saint Vincent's Hospital: 2 p.m., "Pyogenic Infections", Students' Lecture Room, Dr. C. P. Reilly; 3 p.m., demonstration of cases, out-patient department, Dr. W. Keith Myers; 4.30 p.m., "Pityriasis Rosea, Granuloma Annulare and Virus Infections", Students' Lecture Room, Dr. F. J. Collett.

Thursday, August 30: At the Sydney Hospital: 2 p.m., "Seborrhœic Dermatitis, Acne *et cetera*", Maitland Lecture Theatre, Dr. Ewan Murray-Will; 3 p.m., demonstration of cases, out-patient department, Dr. A. Geoffrey Finley; 4.30 p.m., "Drug Eruptions", Maitland Lecture Theatre, Dr. J. M. Rae.

Friday, August 31: At the Royal Prince Alfred Hospital: 2 p.m., demonstration of cases, out-patient department, Dr. Richard B. Perkins. In the Number 2 Lecture Theatre, New Medical School: 3.30 p.m., "Malignant Tumours of the Skin", Dr. J. C. Belisario; 4.30 p.m., round table conference—chairman, Dr. J. C. Belisario.

The fee for attendance is £6 6s., and the closing date for applications is August 20, 1956.

#### Method of Enrolment.

Early written application, with remittance, should be made to the Course Secretary, The Post-Graduate Committee in Medicine, 131 Macquarie Street, Sydney, from whom programmes may be obtained. Telephones: BU 4497-8. Telegraphic address: "Postgrad Sydney."

#### Taxation Deductions.

A deduction may be claimed in respect of fees paid for attendance at courses held under the Committee's auspices when such fees are paid by medical practitioners who are in practice. Travelling expenses incurred in attending such courses may also be claimed. When such deductions are claimed, "Taxation-File No.AF/1865" should be quoted.

#### Examination Results.

The Post-Graduate Committee in Medicine in the University of Sydney announces that the undermentioned candidates satisfied the examiners at the recent examinations for Part II of the following medical diplomas of the University of Sydney: Anæsthesia: B. S. Clifton, Jeanne M. Collison, B. W. Gunner, K. W. McLeod, E. H. Morgan, B. J. Pollard, B. White. Dermatological medicine: D. A. W. Downie, B. R. Entwisle, A. C. Green, B. McGaw, E. H. Taft. Gynæcology and obstetrics: P. M. Elliott. Laryngology and otorhinology: B. P. Scrivener. Ophthalmology: P. F. Anderson, P. H. Hanbury, J. S. Rogers, R. W. Winn. Psychological medicine: Clara Campbell, F. J. Kyneur.

## FEDERATION OF COUNTRY LOCAL ASSOCIATIONS (NEW SOUTH WALES).

#### Post-Graduate Week at Lismore.

THE fifth annual post-graduate week of the Federation of Country Local Associations is to be held at Lismore from August 13 to 17, 1956. The emphasis in these courses is on the work of the country general practitioners, and with the assistance of the Post-Graduate Committee in Medicine in the University of Sydney FOCLA plans to make the Lismore week as successful as previous courses. Details of the programme were published in the issue of April 28, 1956. Information regarding travel facilities and accommodation may be obtained from the Course Secretary, Dr. N. Kerkenezov, 96 Molesworth Street, Lismore. Teilephone: 960. The North-Eastern Medical Association extends to those interested an invitation to visit the "north coast".

## Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Eggins, Barrie James, M.B., B.S., 1950 (Univ. Sydney), 35 Dalley Street, Lismore, New South Wales.

## Deaths.

THE following death has been announced:

EDDY.—Cecil Ernest Eddy, on June 27, 1956, at Perth.

## Diary for the Month.

JULY 10.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
JULY 10.—New South Wales Branch, B.M.A.: Organization and Science Committee.
JULY 13.—Tasmanian Branch, B.M.A.: Council Meeting.
JULY 13.—Queensland Branch, B.M.A.: Council Meeting.
JULY 16.—Victorian Branch, B.M.A.: Finance Subcommittee.
JULY 17.—New South Wales Branch, B.M.A.: Medical Politics Committee.
JULY 18.—Western Australian Branch, B.M.A.: General Meeting.
JULY 19.—Victorian Branch, B.M.A.: Executive of Branch Council.
JULY 19.—New South Wales Branch, B.M.A.: Clinical Meeting.
JULY 24.—New South Wales Branch, B.M.A.: Ethics Committee.

## Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

*New South Wales Branch* (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

*Queensland Branch* (Honorary Secretary, B.M.A. House, 225 Wickham Terrace, Brisbane, B17): Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

*South Australian Branch* (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

## Editorial Notices.

MANUSCRIPTS forwarded to the office of this journal cannot under any circumstances be returned. Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary be stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2-3.)

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